

Pulmonary Manifestations of HIV Disease

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1. Introduction

After the first cases of AIDS were described in 1981, the HIV pandemic rapidly expanded to become a major global public health problem with broad health, social, economic and developmental consequences that have not been seen with any other disease. In the 30 years that this disease has been known to mankind it has killed an estimated 25 million people and continues to affect not less than 33 million people many of whom could die if life saving therapies are not made available to them¹. The African continent has borne the largest impact of this disease. Of the 33.3 million people that UNAIDS estimated were living with HIV in 2009, nearly 67% were living in Africa¹.

Pulmonary disease is a major contributor to the morbidity and mortality suffered by persons infected with HIV. It was the appearance of previously rare Pneumocystis pneumonia often accompanied by Kaposi sarcoma in previously healthy young gay men, intravenous drugs addicts and their sexual contacts that alerted the world to the new syndrome of the Acquired Immune Deficiency Syndrome (AIDS) caused by HIV^{2,3,4,5,6}. Before combination anti retroviral treatment (cART) became available a high proportion of HIV infected individuals would experience respiratory symptoms, and serious life threatening lung disease. Lung disease was often the index diagnosis that would point to the presence of HIV infection^{7,8}. In general the incidence of serious pulmonary disease has declined following the wide availability of cART. For example in the USA rates of opportunistic infections decreased from 89.0 per 1000 person years in 1994-1997 to 25 per 1000 person years in 1998-2002, and 13 per 1000 person years in 2003-2007⁹. However, the incidence of many infectious diseases remain relatively high even in the cART era^{10,11} and worryingly as HIV infected persons live longer, they appear to face an increased risk of non infectious lung diseases such as lung cancer, chronic obstructive lung disease and pulmonary arterial hypertension^{12,13}.

The range of pulmonary diseases that occur in HIV infected individuals is wide and includes infections, neoplasms, vascular lesions, interstitial pneumonias and obstructive airways disease. This chapter will summarize the current knowledge base on HIV associated lung disease including the burden and spectrum of the common diseases, diagnostic evaluation and approaches to treatment and prevention.

2. Burden of pulmonary disease in HIV

Prospective cohort studies carried out in the pre cART era out in North America and Western Europe documented a high incidence of both Pneumocystis and bacterial

Pneumonia	Bacterial	Streptococcus pneumoniae Haemophilus influenza Staphylococcus aureus Pseudomonas aeruginosa Mycobacterium tuberculosis Others
	Fungal	Pneumocystis jirovecii Aspergillus spp Cryptococcus neoformans Candida spp Mycoses Endemic to specific geographic areas (Histoplasma spp, Coccidioides spp, Paracoccidioides, Pencillium marneffeii)
	Viral	Cytomegalovirus Herpes Simplex Influenza Others
	Parastic	Toxoplasma gondii Strongyloides stercoralis
Malignancies		Kaposi sarcoma Lymphoma Lung cancer
Other non infectious diseases		Non specific Interstitial pneumonitis Lymphoid Intersitial Pneumonitis Pulmonary arterial hypertension Chronic Obstructive Airway disease Others

Table 1. Common pulmonary complications of HIV/AIDS.

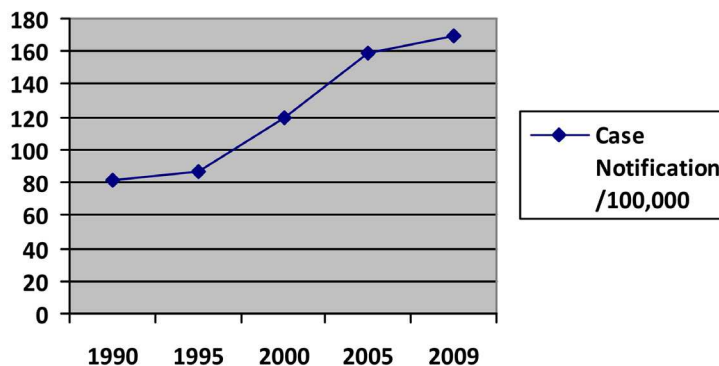
pneumonia^{14,15}. The advent of cART markedly reduced the burden of both Pneumocystis and bacterial pneumonia but more so for Pneumocystis pneumonia^{16,17,18}.

In contra distinction with situation in the developed world where Pneumocystis pneumonia was the hallmark of HIV lung disease, tuberculosis (TB) has been the predominant disease in HIV infected persons in Sub - Saharan Africa. Tuberculosis case notification rates rapidly escalated as the HIV epidemic spread^{19, 20, 21}. In 2009 the World Health Organization estimated that HIV associated TB occurred in about 1.2 million people and was responsible for the deaths of about 200,000 people with nearly 85% of this burden occurring in Sub - Saharan Africa²².

3. Clinical evaluation of HIV infected persons with respiratory symptoms

3.1 History

Even though advances have been made in medical technologies for the diagnosis of lung disease, a good clinical history remains essential in the clinical evaluation of HIV infected persons with lung disease. A thorough understanding of the patient's illness may assist to narrow down the specific diagnosis behind the patient symptoms. It is important to establish if the patient presenting with respiratory symptoms already knows his or her HIV status and



Source WHO, Global Tuberculosis Report, 2010

Fig. 1. TB Case Notification in Sub-Saharan Africa - 1990-2009.

if so how long that status has been known. It is also important to know if that person has suffered opportunistic infections in the past, and if the patient is taking cART and preventive therapy for opportunistic infections. If the patient has been taking cART current and previous regimens must be elucidated and enquiries on adherence to current and previous cART made. The appearance of a lung opportunistic infection in a patient who has been on cART may point to a failing regimen. Since certain infections occur only in specific geographic areas a travel history should be obtained. Other risk factors for disease occurrence or for poor outcomes must as far as feasible be sought. These risk factors include intravenous drug use, alcohol abuse and tobacco smoking. The pre morbid health status must also be known.

3.2 Clinical examination

The clinical examination is intended to establish if serious lung disease is present and thus if urgent interventions are required. A common sense approach will help identify most patients with serious lung disease. Assessment of the patients' mental status together with measurement of the respiratory rate, pulse, temperature, blood pressure and transcutaneous arterial oxygen saturation should rapidly reveal the presence or absence of serious life threatening lung disease.

3.3 Laboratory tests

The choice of laboratory and other tests to be carried out will depend on the clinical condition of the patient, the setting in which the patient is seen and the laboratory infrastructure available. Ideally most patients should have a plain chest radiograph to confirm the presence of lung disease and the extent of pulmonary involvement which will influence the placement of patients into specific risk groups for various outcomes and guide further management. Further medical tests may be carried out to identify co-morbid states or other organ involvement to assist with prognostication while others may be carried to diagnose the specific disease and thus assist in provision of targeted treatment. Tests designed to identify specific diseases include examination of body fluids such as sputum, blood, urine, bronchoalveolar lavage fluid, pleural fluid and others for pathogens using various stains, cultures, antigen and nucleic acid detection tests. Fiberoptic bronchoscopy (FOB), where available, with lavage, brushing and biopsy has found a special place in the evaluation of HIV infected persons with

respiratory symptoms. However FOB should not be used routinely in all HIV infected persons. This procedure may not provide treatment changing results in some settings.

Evaluation of the patient with HIV Lung Disease

Test/procedure	Purpose	Comment
Chest x-ray	Detection of lung disease/ severity assessment	Universally done
CT scan	Detection of lung disease /severity assessment	Offers better detection and radiographic characterization of lung disease/May be abnormal in the presence of a normal chest x-ray
Pulse oximetry	Severity assessment/ monitoring	Should be used in all patients with severe disease
Arterial blood gases	Severity assessment/ monitoring	Should be used in all patients with severe disease
Blood count (WBC, HB, Platelets)/ coagulation tests	Severity assessment/ monitoring	Should be used in all patients with severe disease
Renal and liver function tests	Severity assessment/ monitoring	Should be used in all patients with severe disease
Induced Sputum gram stain and culture	Microbiological aetiology	Should be used in all patients with severe disease
Blood culture	Microbiological aetiology	Should be used in all patients with severe disease
Antigen detection (Blood/urine/sputum)	Microbiological aetiology	Especially for S. Pneumoniae and L. pneumophila sero group 1
Serological tests	Microbiological aetiology	Most for the detection of "atypical pathogens". Provide retrospective diagnosis
Fiberoptic bronchoscopy with lavage, brushing and or biopsy	Microbiological aetiology/ diagnosis of non infectious disease	Probably best reserved for patients with non diagnostic results with non invasive tests
Open Lung Biopsy	Histological diagnosis/Microbiological diagnosis	Used mostly if bronchoscopy with TBB fails to provide a diagnosis
Radio isotope studies	Diagnosis of infectious /non infectious disease	Gallium 67 citrate and ^{99m} TCDTPA: expensive, time consuming and require complex infrastructure
Other tests (lung function tests)	Diagnosis of non infectious disease (COPD)	TLCO, KCO, FEV1, FVC: Sensitive but not specific for any lung disease

Table 2. Common tests and procedures for evaluating HIV associated lung disease.

4. Specific lung diseases

4.1 Fungal pneumonia in HIV infected persons

4.1.1 Pneumocystis pneumonia (PcP)

The causative organism of Pneumocystis pneumonia, *Pneumocystis jirovecii*, has had an interesting history in terms of its taxonomy. Initially the pathogen was thought to be protozoan in nature. Later it was placed on the fungal group based on its nucleic acid profile and the name of the human pathogen was changed from *Pneumocystis carinii* to *Pneumocystis jirovecii* based on the understanding that the species that affects humans is distinctly different from that which affects other animals including cats²³.

4.1.1.1 Epidemiology

Pneumocystis pneumonia was the dominant opportunistic infection in the pre cART era in the North America and Europe^{1, 2, 3,4,5,14,15}. In contrast to the dominance of PcP in North America and Western Europe, other regions of the world and especially Sub Saharan Africa, the current epicentre of the HIV/AIDS epidemic, did not experience this surge of PcP with rates of PcP ranging from 0- 21% in the earlier case series and cohort studies^{24,25,26,27}. In fact for a while this infection was thought to be absent from Africa²⁸. As the HIV epidemic matured in Sub-Saharan Africa the prevalence of PcP in HIV infected patients appeared to have increased^{29,30,31}, but the rates of this infection did not reach the levels that were observed in Western Europe and North America during the early years of the HIV epidemic. Currently PcP remains relatively rare in Sub - Saharan Africa, with prevalence as low as 1% being reported^{32, 33, 34}. The reasons for the low prevalence of PcP in Sub - Saharan Africa are not fully known but racial factors influencing susceptibility to the development of disease following infection or colonization may partly play a role. It is also worth noting that African populations have been documented to have a high prevalence of exposure to this pathogen and therefore the low rates of PcP in Sub -Saharan Africa is not the result of the absence of the pathogen from the African environment³⁵.

4.1.1.2 Risk factors

Several studies have examined the risk factors for PcP in HIV infected individuals. These studies indicate that the risk of PcP is highest in those with declining CD 4 T cell count especially when the count falls below 200, unexplained fever, history of AIDS defining illness, presence of oral thrush and not being on prophylaxis or when prophylaxis fails^{36,37}. HIV infected persons of the negroid race may have a lower risk of of PcP compared to Caucasians³⁸.

4.1.1.3 Clinical manifestations

Symptoms

Pneumocystis pneumonia usually presents with a sub acute onset of cough and shortness of breath. The cough is usually non productive or may be productive of scanty mucoid sputum while shortness of breath is slowly progressive and gradually limits activity. Many patients do not experience chest pain and do not have other constitutional disturbances, the symptom complex being largely dominated by shortness of breath.

Signs

The majority of patients will appear anxious when they are first examined. The breathing frequency is usually rapid and shallow. The pulse is also rapid but most often at the first evaluation the blood pressure is normal. Patients with PcP may have no fever at

presentation. Lung signs including crackles may be absent and even when present are non specific. There may be evidence of other opportunistic infections such as ano genital herpetic ulcers and oral thrush.



Fig. 2. Ano genital Herpetic Ulcers in a patient with PcP.

4.1.1.4 Pneumocystis pneumonia - Diagnostic tests

Radiologic imaging

Patients suspected to have PcP should have a chest radiograph which typically shows bilateral interstitial or alveolar shadows in the mid zones with basal and apical sparing. In some situations PcP may be present without any obvious changes on the chest radiograph. In these situations high resolution chest CT scan may reveal typical abnormalities that may render the performance of a fiberoptic bronchoscopy procedure unwarranted³⁹. Radiostopic studies using Gallium 67 scintigraphy, where available may help to distinguish lung infections from neoplastic and other diseases processes⁴⁰.

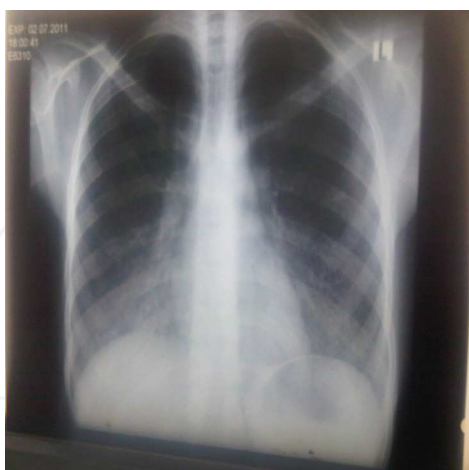


Fig. 3. Chest Radiograph showing shadows typical of PcP.

Lung function testing

Patients with PcP typically are hypoxemic and will desaturate further when exercised, an observation that has been used as a diagnostic test to predict the presence of this infection ⁴¹,

42. The measurement of diffusion capacity has also been found to be a useful diagnostic test⁴³.

Microbiological tests

The definitive diagnosis of PcP is based on the identification of the pathogen in lung samples most commonly obtained through induced sputum, fiberoptic bronchoscopy or open lung biopsy. While some controversy still exists, fiberoptic bronchoscopy with lavage is the standard procedure for the detection of *Pneumocystis jirovecii*⁴⁴. Both bronchial brushings and transbronchial biopsy during the bronchoscopy procedure may offer no added value in the evaluation of patients suspected to have PcP⁴⁵. In general lower respiratory tract specimens are subjected to either cytochemical staining using May-Grünwald-Giemsa (MGG), toluidine blue-O (TOL), Papanicolaou (PAP) and Grocott methenamine silver (GRO); immunofluorescent staining with monoclonal antibodies or PCR. However PCR may not distinguish infection from colonization⁴⁶. Examination of expectorated sputum remains a useful procedure for the microbiological diagnosis of PcP especially in low resource settings. When toluidine blue O staining of expectorated sputum is carried out the sensitivity approaches 70% and 35% compared with immunofluorescent staining and PCR respectively while specificity is 100% and thus in these settings examination of expectorated sputum may be a practical procedure for the diagnosis of PcP⁴⁷. The yield from sputum examination may be increased if sputum production is induced following inhalation of hypertonic saline. In a meta analysis of diagnostic procedures for PcP, it was found that, compared with bronchoalveolar lavage as the gold standard, examination of induced sputum had an overall sensitivity of 55.5% and a specificity of 98.6% with even better sensitivity at 67% versus 43.1% when comparing immunofluorescent staining with cytochemical staining. In settings where the prevalence of PcP is in the range of 25-60%, the positive and negative predictive values ranged from 86-96.7% and 66.2-89.8%, respectively, with immunofluorescent staining, and 79-94.4% and 53-83.5% with cytochemical staining⁴⁸.

Other tests

The diagnosis of PcP may also be aided by the measurement of serum 1-3 beta D -Glucan, a cell wall component of most pathogenic fungi including *Pneumocystis jirovecii* which has been found to have a sensitivity of nearly 100% and specificity of about 96.4%. Therefore this test may be used as non invasive test for diagnosis of PcP^{49,50}. This test may however not correlate with disease severity and should not be used to monitor patients on treatment⁸⁷.

Treatment of Pneumocystis Pneumonia

The drug of first choice for the treatment of PcP remains cotrimoxazole. The recommended dose is 20mg per Kg body weight per day for the trimethoprim and 100 mg per Kg per day for the sulphamethoxazole, given in three or four divided doses. It has been reported, however that lower doses may be used without loss of efficacy and with the added advantage of a reduction in the rate of adverse events⁵¹. Second line treatment options for patients unable to tolerate high dose cotrimoxazole include clindamycin /primaquine and pentamidine but pentamidine may be associated with a greater risk of death⁵². Trimetrexate with folinic acid is generally well tolerated and has a clinical efficacy of about 70%⁵³. Other second line therapies include atovaquone, dapsone, a combination product of trimethoprim and dapsone and eflornithine hydrochloride. A metanalysis of second line therapies, in patients who fail whatever initial treatment is given concluded that the combination of

clindamycin plus primaquine appears to be the most effective alternative treatment for patients with PcP who are unresponsive to conventional antipneumocystis agents⁵⁴.

Outcomes

Pneumocystis pneumonia is a serious life threatening illness in persons living with HIV. The overall in hospital mortality of this illness is in the region of 10-13%. Among the factors that have been associated with death in patients with PcP include older age, recent injection drug use, total bilirubin of greater than 0.6 mg/dl, serum albumin of less than 3 g/dl, alveolar-arterial oxygen gradient of equal or greater than 50 mm Hg, failure of cotrimoxazole treatment and the presence of co- morbidities such as bacterial pneumonia, Kaposi sarcoma and TB^{55,56,57}. Patients who need to be admitted to the intensive care unit may suffer very high rates of deaths that could reach 80% within the ICU and up to 34 % three months post ICU admission⁵⁸. The high mortality of patients who need to be mechanically ventilated appears to be associated with high APACHE II scores, high levels of Positive End Expiratory Pressures (PEEP), the presence of co- infection with CMV and lower CD 4 T cell counts ^{59,60}.

In an attempt to lower the mortality of PcP adjunctive systemic steroids are recommended⁶¹ based on the results of clinical trials that documented a reduction in mortality in patients with moderate to severe disease^{62,63,64}. Use of adjunctive steroids for the treatment of moderate to severe PcP has not been associated with increased long term mortality after the PcP episode nor with an increase in the incidence of other opportunistic infections^{65,66}.

There have been concerns that patients infected with *Pneumocystis jirovecii* that has developed mutations in the dihydropteroate synthase reductase gene may not respond as well to cotrimoxazole as patients whose pathogen does not carry these mutations. The majority of studies however indicate that the development of mutations on the dihydropteroate synthase reductase gene does not have an impact on the efficacy of cotrimoxazole in the treatment of PcP^{67,68}. However it has been reported that DHPS mutations increase the risk of death in patients with PcP ⁶⁹.

It has been suggested that measurement of C- Reactive Protein (CRP) may be a useful prognostic marker in patients with PcP. In one study the levels of CRP were negatively correlated with arterial oxygenation (PaO₂)⁷⁰.

Prevention

Pneumocystis pneumonia in HIV infected persons is a preventable disease. The most effective treatment for the prevention of PcP is cART which reconstitutes the immune system and dramatically reduces the incidence of opportunistic infections including PcP^{16, 17, 18, 19}. Many HIV infected persons with risk factors for PcP will however require to be protected from this disease even if they have been placed on cART until CD4 T cell recovery has taken place. Although aerosolized pentamidine and cotrimoxazole may have equal efficacy⁷¹, the preferred drug is cotrimoxazole⁷² but if this cannot be tolerated aerosolized pentamidine or atovaquone which have been found to have similar efficacy may be used⁷³. Mutation in the dihydrofolate reductase gene may however, lead to prophylaxis failures^{74,75}. An alternative drug is dapsone which appears to have an efficacy equal to that of atovaquone but which may be less safe⁷⁶. In patients receiving cART it has been recommended that prophylaxis for PcP be discontinued when the CD 4 T cell count climbs to 200 and above⁷⁷ but recent studies suggest that prophylaxis may be discontinued when viral suppression is achieved and before the CD 4 T cell count reaches 200 and above^{78,79}. These are reassuring observations because cotrimoxazole treatment may sometimes be associated serious life threatening complications including septic shock like syndrome⁸⁰.

Complications

Pneumocystis pneumonia may result in pneumothorax and pneumomediastinum both of which may be life threatening. These complications are thought to arise from newly formed cysts and bronchiectasis⁸¹

4.1.2 Other fungal pneumonias in HIV infected persons

Pneumonia caused by fungal pathogens, other than *Pneumocystis jirovecii*, though less common when compared with PcP and bacterial pneumonia is a frequent cause of morbidity and mortality in HIV infected persons. Fungal pathogens have been identified mostly in severely immunocompromised patients with CD 4 T cell count below 200 and the lung is often involved in a disease process that is often disseminated and or where multiple pathogens are causing disease. The mortality of fungal pneumonia in HIV infected persons is thus high.

Of the fungal pathogens that have been associated with lung disease in persons living with HIV *Cryptococcus* may not only be the commonest pathogen but also the best characterized. This fungus is ubiquitous and is more famous for causing meningitis in severely immunocompromised patients. Lung disease due to *Cryptococcus neoformans* has been reported in all parts of the world and tends to occur in patients who have CD 4 T cell counts below 200^{82,83,84}. The other ubiquitous fungus that has been associated with lung disease in HIV infected persons is *Aspergillus* spp. Invasive Aspergillosis occurs most commonly in patients who have a severely depressed immune system and often participates in disease in partnership with other pathogens, as a disseminated infection which confers a high mortality^{85,86,87}. Other fungal pathogens are mostly confined to specific geographic areas where they have been reported to cause significant morbidity and mortality in HIV infected persons. These fungal pathogens include *Histoplasma* spp, *Coccidioides* spp, *Paracoccidioides* spp, *Penicillium marneffe*, *Sporotrichosis* spp and *Blastomycosis*^{88,89,90}.

4.1.2.1 Clinical manifestations

Pneumonia due to fungal pathogens, other than PcP, may follow an acute or sub acute course. The disease may be indistinguishable from pneumonia due to bacterial pathogens and TB. There are no clinical features that distinguish fungal pneumonia from pneumonia due to other pathogens. As in other forms of pneumonia the clinical syndrome is characterized by the presence of a cough, shortness of breath and fever as the primary symptoms. In the presence of disseminated disease or meningitis, headache, malaise, vomiting, confusion and wasting may be present. Specific examination of the chest may reveal tachypnea, signs of consolidation or the presence of a pleural effusion while chest radiography may reveal segmental, lobar or multi lobar consolidation, pleural effusion and or widespread reticular, nodular, reticulo - nodular or mixed alveolar and interstitial shadowing.

4.1.2.2 Diagnosis

The diagnosis of fungal pneumonia is based on the identification of fungal pathogens in respiratory specimens mostly obtained at fiberoptic bronchoscopy with bronchoalveolar lavage, bronchial brushings or occasionally through biopsies. To confirm a fungal pathogen the lung specimens are cultured in Sabborauds media or subjected to PCR. For Cryptococcal disease measurement of serum Cryptococcal antigen may be yield positive results, especially when the disease is disseminated. Cryptococcal antigen in serum may be negative in isolated pulmonary disease.

4.1.2.3 Treatment

The treatment of fungal pneumonia is dependent on the specific pathogen. Many classes of antifungal agents are now available for the treatment of serious fungal infections such as pneumonia. These include polyene antifungals such as amphotericin B, imidazole, triazole and thiazole antifungals such as ketoconazole, fluconazole and itraconazole and echinocandins such as caspofungin, micafungin and anidulafungin

4.1.2.4 Prevention

The most important intervention for the prevention of fungal pneumonia is immune reconstitution using cART. While fluconazole has been used to prevent Cryptococcal infections in HIV infected persons it has not found widespread use and the efficacy may be suboptimal⁹¹.

4.2 Community Acquired Bacterial Pneumonia (CABP) in HIV infected persons

4.2.1 Epidemiology

Persons living with HIV have a high incidence of community acquired bacterial pneumonia⁹². Often CABP is the index diagnosis for HIV^{93,94}. With the advent of cART, the incidence of CABP fell but not as much as that of PcP in high income countries probably as a result of the presence of other risk factors that drive the susceptibility to bacterial pneumonia such as intravenous drugs use, smoking and alcohol abuse among HIV infected individuals^{95,96,97}. In one French study, CABP was the cause of admission to the intensive care unit in 74% of 147 HIV infected patients admitted to ICU and surpassed PcP as the predominant cause of acute respiratory failure in the era of cART⁹⁸. In African HIV infected patients CABP and in particular pneumococcal disease remains a major cause of morbidity and mortality. Autopsy studies have also documented high rates of bacterial pneumonia in HIV patients dying of lung disease. For example in one Brazilian autopsy study involving 240 HIV infected patients dying of respiratory failure, the cause of death was attributed to CABP in 36 %⁹⁹. In a similar study from one USA centre, 47 patients with a pre mortem diagnosis of TB, CABP was deemed to have been the cause of death in 13 (26%)¹⁰⁰.

The incidence of lower respiratory tract infection increases as the CD4 T cell count declines and in the absence of ART. Acute bronchitis, CABP and PcP will be experienced by more than 80% of patients with a CD 4 T cell count of less than 200 even when these patients are provided with chemoprophylaxis¹⁰¹. Injecting drug users have an increased incidence of BP compared with other categories of HIV acquisition as are patients who smoke tobacco, have liver cirrhosis and have suffered a previous episodes of BP^{102,103}. Smoking cessation has been found to be beneficial in reducing the incidence of BP in HIV infected persons^{104,105,106}. Other factors that increase the risk of BP and in particular pneumococcal pneumonia include age, not being on HAART¹⁰⁷ and neutropenia¹⁰⁸. On the other hand the major risk factor for nosocomial pneumonia is the duration of hospitalization^{109,110}. The pathogens commonly encountered in nosocomial pneumonia include *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Streptococcus pneumoniae*.

4.2.2 Clinical manifestations

Community acquired bacterial pneumonia is largely an acute illness in which symptoms evolve rapidly over a few days¹¹¹. The classical symptoms include cough with or without sputum expectoration, chest pain which is often pleuritic in nature, difficulties in breathing

and rapid breathing primarily driven by the chest pain and fever. Clinical examination usually reveals a sickly patient who is febrile, tachypneic but usually not as tachypneic as the patient with PcP and who has a tachycardia. Specific examination of the chest may reveal dullness to percussion, with bronchial breath sounds and pulmonary rales over the affected lobe or lobes of the lungs.

4.2.3 Imaging

A plain chest radiograph should be obtained in all patients suspected to have bacterial pneumonia. The plain chest x-ray typically shows alveolar shadows with segmental, lobar or bronchopneumonic distribution and these changes are similar to those seen in HIV sero negative patients¹¹². Although diffuse interstitial shadowing is less common this radiographic picture should not be used to exclude BP. Other changes that may be visible on the chest radiograph include the presence of pleural effusions and cavitations. No radiographic appearance is pathognomonic of any specific pathogen. The chest x-ray in BP is largely uninfluenced by cART but patients with CD 4 T cell count less than 200 are likely to have a bronchopneumonic picture. It has also been documented that bacteremic patients were more likely to have a lobar lesion and a higher CD4 T cell count above 200^{113,114}. A chest CT scan may be very helpful. It may reveal lesions where the plain chest x-ray does not and have high specificity for certain infections such PcP¹¹⁵.

4.2.4 Laboratory tests

In hospitalized patients with CABP total white blood cell count, should be measured. A total white cell count of below 4×10^9 /L has been associated with bacteraemia and excess mortality in HIV negative patients with community acquired pneumonia¹¹⁶ and may carry the same risk in HIV infected persons¹¹⁷. Similarly thrombocytopenia (count of less than $100,000 \times 10^9$ /l) appears to signify severe disease that necessitates aggressive treatment including admission to the intensive care unit¹¹⁸. Measurement of the CRP has not been documented to be able to discriminate between PcP and BP¹¹⁹, however, using the cut off value of 3ng/ml for procalcitonin and 246 mg/l for CRP one group of investigators reported an increased capability to distinguish BP from TB with a sensitivity of 81.8% and a specificity of 82.5% for the procalcitonin and 78.8% and 82.3% respectively for the CRP¹²⁰.

In hospitalized patients the measurement of blood urea, creatinine, sugar, albumin, bilirubin, AST and ALT helps to place patients in specific risk groups for poor outcomes using the CURB - 65¹²¹ and or Pneumonia Severity Index criteria¹²²

The microbiological diagnosis of CABP is dependent on the detection of the pathogen itself in culture, components of the pathogen (antigen) in body fluids or the antibody response to the pathogen. Relevant samples where the pathogen or its antigen may be identified include sputum, bronchoalveolar lavage fluid, bronchial brushings, lung biopsies or aspirates, blood, urine and pleural fluid. The interpretation of microbiological culture results from sputum and other respiratory secretions is hampered by the contamination of these samples by oropharyngeal bacterial colonizers and precautions must be taken to ensure that not only are good quality specimens obtained but also appropriate and proven methods for interpreting results of bacterial cultures from these specimens are followed. A good quality sputum sample is for example one that has low number of squamous cells and high number of polymorphonuclear cells¹²³.

4.2.5 Sputum microbiologic testing

In hospitalized patients, as far as feasible, sputum samples should be collected for gram staining and bacterial culture. If a sputum gram stain reveals a predominance of a pathogen with specific staining and morphological features (e.g. gram positive diplococci) this is highly predictive of the pathogen that is responsible for that episode of pneumonia. The sensitivity of sputum gram stain may reach 58%¹²⁴. Sputum bacterial culture may be diagnostic in up to 34% of pneumonia episodes and be correlated with the organism isolated from a sterile site¹²⁵. Compared with BAL and TBB the sensitivity and specificity of induced sputum is about 60% and 40% respectively¹²⁶. Using quantitative bacterial culture the cut off for significant bacterial growth is usually considered to be 10^5 colony forming units per ml of sputum. In settings where PcP incidence may be low the fiberoptic bronchoscopy procedure may add little value to the examination of sputum for other pathogens¹²⁷.

4.2.6 Urinary antigen testing

Urinary antigen tests are available for two bacterial pathogens: *Streptococcus pneumoniae* and *Legionella pneumophila* sero group 1. The urinary pneumococcal antigen test is a rapid test with good test performance parameters including a sensitivity in the region of 81%, specificity 98%, positive (PPV) and negative predictive values (NPV) 98%, and 82%, respectively¹³⁷. The urine pneumococcal antigen test may be positive many weeks after the pneumonia has resolved¹²⁸. The urinary antigen test for *Legionella pneumophila* sero group 1 has a sensitivity of 70-90% and a specificity of nearly 100% for the detection of this pathogen¹²⁹

4.2.7 Serological tests

These tests are used primarily for the detection of atypical pathogens such as *Mycoplasma pneumoniae*¹³⁰, *Chlamydia* Spp and *Legionella* Spp other than *Pneumophila* Sero group 1. The major draw back is that interpretation often requires comparison of results of acute and convalescent sera and thus may not be useful for clinical decision making.

4.2.8 Fiberoptic bronchoscopy

Fiberoptic bronchoscopy is a commonly used procedure for the evaluation of respiratory symptoms in HIV infected persons. Although the diagnostic yield may reach 74% only about 25% of bronchoscopies yield useful results that lead to a change in diagnosis and therapy^{131,132,133}. In situations where there are low rates of PcP and Kaposi sarcoma the fiberoptic bronchoscopy procedure may not yield additional results from that obtained through examination of expectorated sputum and other easily obtained body fluids^{145, 134}, and therefore in such settings this procedure should be used judiciously.

4.2.9 Fine needle transthoracic biopsy/aspiration

This may be an underutilized procedure for the evaluation of respiratory symptoms in patients infected with HIV. The suitable patient for this procedure has a peripheral lesion close to the pleural membrane. The common complication with this procedure is pneumothorax which rarely requires pleural drainage¹³⁵.

4.2.10 The range of pathogens

The range of pathogens involved in CABP in HIV infected persons is wide but the most common pathogens include *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Klebsiella*

pneumoniae, *Haemophilus influenzae*, *H. parainfluenzae* and *Pseudomonas aeruginosa*. *Streptococcus pneumoniae* is the most common pathogen isolated in 40- 60% of bacteriologically confirmed cases^{136,137,138}. In TB endemic areas TB is a common cause of acute community acquired pneumonia and should always be screened for in all patients presenting with this condition.

Persons living with HIV are at increased risk of pneumococcal bacteraemia associated with community acquired pneumonia^{139,140,141}. However the impact of the bacteraemia on survival appears to be uncertain with some studies suggesting there is no increase in the risk of mortality while others have found an association between pneumococcal bacteraemia and mortality from community acquired pneumonia^{142,154,155}. Compared with sero negative patients HIV infected patients may be predisposed to harbouring penicillin resistant pneumococci^{155,143}.

Other pathogens that have been identified in HIV infected patients with community acquired pneumonia include:

- *Rhodococcus equi*, a gram-positive, coryneform bacterium that causes zoonotic infection mainly in horses and foals. Most cases have been reported in case reports and or case series^{144, 145,146},
- *Enterococcus* that may be vancomycin resistant and associated with lung abscess and empyema¹⁴⁷
- *Nocardia asteroides* a gram positive filamentous rod which may cause chronic lung infection and may sometimes disseminate with associated high mortality^{148,149}. This infection may be difficult to diagnose.
- *Legionella pneumophila*, although it remains unclear if HIV infected persons are at increased risk of infection or severe disease^{150 151}
- *Mycoplasma pneumoniae* which has been found in up to 17% of patients with community acquired pneumonia in both HIV negative and positive persons^{152, 153}.
- *Moraxella catarrhalis* though this pathogen appears to be an uncommon cause of community acquired pneumonia. In one large study only 4 cases among 2123 patients hospitalized over a nine year period were found to have this pathogen¹⁵⁴
- Community acquired *Pseudomonas aeruginosa* which has been described as a cause of severe and often fulminant community acquired pneumonia in patients who are severely immune suppressed and who may not have the traditional risk factors for this infection such as central lines and neutropenia^{155,156, 157}.
- *Salmonella* which has been described mainly in patients with *Salmonella* bacteraemia¹⁵⁸.

Often the HIV infected person has multiple pathogens causing the respiratory illness^{159, 160, 161, 162} such as fungi, bacterial and viral pathogens.

4.2.11 Treatment of community acquired bacterial pneumonia in HIV infected persons

A holistic approach should be adopted to the care of HIV infected patients with community acquired pneumonia. The benefit of targeted anti microbial therapy are likely to accrue if attention is paid to hydration, oxygenation and nutritional needs among other needs of the patient. Control of symptoms such as pain, fever, vomiting and diarrhoea which often are part of the pneumonia syndrome in HIV infected persons will ensure patient comfort as specific antimicrobial treatment takes effect.

The initial antimicrobial treatment will usually be chosen on an empiric basis and this choice should be based on the range of common pathogens isolated in the specific setting, the anti

microbial susceptibility patterns of common pathogens, the cost of treatment, co morbid states and to some extent the experience of the treating practitioner. No studies have specifically examined the efficacy of various antibiotics for the management of CABP in HIV infected persons. Thus current practice is based largely on guidelines derived from studies involving HIV sero negative individuals and clinical experience. In TB endemic settings the combination of a beta lactam and a macrolides is preferred over the use of fluoroquinolones to avoid masking TB. The combination of a beta lactam and a macrolide has been associated with better outcomes in HIV sero negative patients, but not in all studies¹⁶³, and is recommended by the Infectious Disease Society of America and the American Thoracic Society¹⁶⁴. Pneumococcal penicillin resistance may be more common in HIV infected persons¹⁶⁵ but outcomes of treatment appear not to be influenced by the presence of intermediate levels of penicillin resistance^{166, 167}.

In patients with *Rhodococcus* infection at least two antimicrobial agents should be given simultaneously to treat this infection for a period of up to several months. The combinations of erythromycin and rifampin or imipenem and teicoplanin have been found to be the most effective treatments in *Rhodococcus* infections¹⁶⁸.

The anti microbial treatment of *Nocardia asteroides* involves the use of combinations with proven synergy, such as imipenem and amikacin, as the recommended initial therapy.

4.2.12 Outcomes of community acquired bacterial pneumonia

Several risk factors may work together to increase the risk of death in HIV infected patients receiving treatment for CABP. These risk factors include not being on ART, presence of pneumococcal antigen in urine for patients with pneumococcal pneumonia¹⁶⁹ and comorbid states such as liver cirrhosis (mostly from alcohol abuse)¹⁷⁰. Compared with HIV sero negative patients and in situations where health care delivery may be described as optimal HIV infection appears not to increase the mortality risk in hospitalized patients with Community Acquired Pneumonia and neither does it lead to prolongation of hospital stay^{171,172}.

In patients with acute respiratory failure admitted to the ICU, the risk of death is related to extent of organ failure such as need for mechanical ventilation and use of vasopressor agents rather than HIV parameters such as CD4 T cell count, HIV plasma viral load or use of ART¹⁷³.

Bacteremic pneumococcal disease may confer a higher mortality risk but this has not been a consistent finding¹⁵⁵⁻¹⁵⁹. Certain pathogens confer a greater risk of death. Compared with *Streptococcus pneumoniae* for example patients with *Legionella*, were found to have a higher risk of death probably from a greater prevalence of co morbid conditions¹⁷⁴. Advancing age and low CD4 T cell count are also risk factors for severe disease and death in HIV infected patients including patients on ART^{175,176}.

It has been proposed that HIV infected patients be placed in a low risk immunosuppressed group for death and that in this group the Pneumonia Severity Index (PSI) can be used to define patients at risk of death similar with the use of this tool to define groups of patients at risk of death in HIV negative patients^{177, 178, 179}.

4.2.13 Prevention

Vaccination is available for *Streptococcus pneumoniae*. The 23 valent polysaccharide vaccine appears to be effective in HIV infected persons in North America for reducing all cause pneumonia but those with plasma viral load of greater than 100,000 may not

benefit^{180,181,182}, but the results of clinical trials have not always been consistent¹⁸³. On the other hand African patients have not been documented to benefit from the 23 valent pneumococcal vaccine, ^{184, 185}. To avoid the sub optimal efficacy of the 23 valent pneumococcal vaccine in African HIV infected persons a conjugate vaccine has been developed. A clinical trial of the 7 valent conjugate vaccine among Malawian patients found a protective efficacy of about 74% for the prevention of recurrent pneumococcal pneumonia ¹⁸⁶. The other intervention available for preventing BP in HIV infected persons is cotrimoxazole preventive therapy which is most effective in those with CD 4 T cell count below 200,^{187,188}.

4.2.14 Other issues

Recent data suggests that recurrent BP may be associated with an increased risk of lung cancer in HIV infected persons probably related to the persistent or recurrent inflammation in the lung¹⁸⁹. Parapneumonic effusions may be more common in HIV infected patients with community acquired pneumonia and patients with parapneumonic effusions may have more severe disease with higher rates of bacteraemia¹⁹⁰.

4.3 Mycobacterial pneumonia in HIV infected persons

4.3.1 Mycobacterium tuberculosis

4.3.1.1 Epidemiology

Tuberculosis is the most common opportunistic infection and the most common cause of death in HIV infected persons. The dramatic increase in the burden of TB in Sub - Saharan Africa has been largely blamed on the HIV epidemic¹⁹¹. However, other than for differences in magnitude, TB is the most common opportunistic infection that is observed in the first three months of initiation of cART in both Sub-Saharan Africa and the industrialized world of North America and Europe^{192,193}. The TB and HIV epidemics are so intricately intertwined in Sub-Saharan Africa that care and control of one must be linked with the prevention and care of the other¹⁹⁴. HIV influences TB by increasing the risk of reactivation of latent TB infection, rapid progression of new TB infection to disease and recurrent disease from both re-infection and relapse¹⁹⁵.

4.3.1.2 Clinical manifestations

Pulmonary tuberculosis is characterized by the sub acute onset of cough with or without the production of sputum associated with systemic symptoms of fever, night sweating and loss of weight. The sputum may be stained with blood. These symptoms are not specific for TB. The only symptoms that are significantly more common in TB than in other patients are night sweats and loss of weight¹⁹⁶. There may also be pleuritic chest pain but shortness of breath is uncommon until the late stages of the disease. The symptoms of TB are largely similar between HIV negative and positive patients, however, depending on the stage of HIV disease, HIV infected persons may have stigmata of the HIV infection such as oropharyngeal candidiasis, oral hairy leukoplakia, a non specific skin rash, cutaneous Kaposi sarcoma and peripheral lymph node enlargement.

There may be no significant signs unearthed on specific examination of the chest and even when present these signs are non specific. The chest radiograph is a sensitive but non specific test for detection of TB in both HIV infected and un infected individuals¹⁹⁷. It may show a variety of lesions which to a large extent depend on the severity of the HIV related immunosuppression. When immune function is still relatively well preserved the classical

upper lobe fibrocavitary shadows may be seen. With advancing immune dysfunction the radiologic shadows become atypical and include mid and lower zone shadows, intrathoracic lymph node enlargement, pleural effusions, miliary shadowing among others lesions^{198, 199}.

4.3.1.3 Diagnosis of pulmonary TB

Most TB occurs in middle and low income countries where conventional light microscopic examination of sputum using the Ziehl Nielsen stain is the primary diagnostic test. The test is rapid, relatively simple, inexpensive and highly specific in these settings, however, this test has provided inconsistent sensitivity results ranging from as low as 20%²⁰⁰ to as high as 80%²⁰¹ in comparison to culture confirmed TB and is more commonly negative in HIV infected individuals compared to HIV negative individuals²⁰². Currently WHO recommends that two sputum specimens are obtained immediately the patient makes contact with the health care system. The examination of a third sputum specimen has not been found to add much value with the incremental yield of the third specimen not exceeding 4%²⁰³. Similarly a morning specimen only marginally increases the diagnostic yield of smear microscopy²⁰⁴ and therefore may not be necessary in the evaluation of patients suspected to have TB. To increase the sensitivity of smear microscopy sputum may be treated with bleach or sodium hydroxide and concentrated by centrifugation, or overnight sedimentation preceded by treatment with ammonium sulphate or bleach²⁰⁵. However the value of these sputum processes in HIV infected persons is not clear. The yield of sputum microscopy is consistently increased by up to 10% using fluorescence microscopy with auramine O or auramine - rhodamine stains²⁰⁶ and recently fluorescence microscopy has been simplified by the development of Light Emitting Diode (LED) Fluorescence microscopy²⁰⁷. The Gold standard for TB diagnosis remains culture on solid or liquid media. Conventional culture on solid or liquid media for the diagnosis of TB is however a slow process that may take too long to reliably influence clinical decisions. The development of rapid liquid culture systems such as the Mycobacterial Growth Inhibitor Tube (MGIT) has improved the turn around time and thus the clinical utility of culture for the diagnosis of TB²⁰⁸. The WHO recently recommended rapid liquid TB culture systems for the diagnosis of TB especially in HIV infected persons²⁰⁹. Although recommended by WHO as a bridge to fully automated liquid culture systems for TB diagnosis, non commercial culture systems such Mycobacteria Observation Drug Susceptibility (MODS), Nitrate Reductase Assays (NRAs), Thin layer Agar (TLA) and Colorimetric Redox Indicators (CRIs) systems do not decrease the time to TB diagnosis and drugs susceptibility results²¹⁰. Even though the PCR technique has been used for a long time for the detection of TB, it is the automated cartridge based nucleic acid detection test called the Xpert MTB/Rif test that has the potential to revolutionize the diagnosis of TB especially in HIV infected persons. This test not only provides the diagnosis of TB in under two hours but also is able to indicate if there is likelihood of multi drug resistant TB based on the detection of mutations that confer rifampicin resistance. Diagnostic studies on this test suggest that it has an overall sensitivity of about 92.2% and a specificity of 99% using a single Xpert test. The sensitivity increases to 97.6% using three Xpert tests. Among HIV positive individuals the overall sensitivity of a single Xpert test has been reported to be about 94% compared to 98% in HIV negative individuals. For the detection of rifampicin resistance the sensitivity of this test is about 98%^{211,212}. This test is now recommended as the initial test for the detection of pulmonary TB in HIV infected persons²¹³. Although several serological tests are commercially available for the detection of TB, none has been found to have a consistently high sensitivity and specificity to replace smear microscopy and their use has recently been discouraged by WHO²¹⁴.

4.3.1.4 Treatment of TB in HIV infected persons

Current treatment of pulmonary TB involves the use of combinations of 5 primary drugs: Isoniazid(H), rifampicin(R), ethambutol(E), pyrazinamide(Z),and streptomycin (S). The WHO and the International Standards of TB Care (ISTC) recommends a rifampicin based regimen made of RHZE given daily for two months followed by RH given daily, or two to three times weekly for six months for previously untreated patients²¹⁵. With this regimen most HIV infected patients get cured with a lower risk of failure, relapse and acquired drug resistance²¹⁶. Patients who have been treated previously must be assessed for risk of drug resistance, investigated for drug resistance using the Xpert MTB/Rif test, rapid molecular based line probe assays and culture, and treated with either primary, first line drugs if no drug resistance exists or with second line drugs if drug resistance, especially multi drug resistant TB, is present²³⁸.

4.3.1.5 Drug resistant TB and HIV

The WHO estimated that there were 400,000 cases of multi drug resistant TB, defined as TB bacilli that are resistant to both R and H, in 2009²¹⁴. Although HIV per se appears not to be a risk factor for MDRTB, a link between MDRTB and HIV has been suggested by epidemiologic data from parts of Eastern Europe²¹⁷. Outbreaks of MDRTB in HIV infected persons have been linked to nosocomial transmission of TB and have in general been characterized by high mortality among affected patients²¹⁸. The more recent reports were from Southern Africa where a large majority of the patients were HIV infected, had extensive drug resistance (MDRTB with additional resistance to a fluoroquinolone and an injectable such as kanamycin, amikacin or capreomycin) and died within a few weeks after the diagnosis of XDRTB²¹⁹, emphasizing the critical role of implementing robust measures to prevent TB transmission in situations where HIV infected persons receive care.

4.3.1.6 Outcomes

HIV infected PTB patients are at increased risk of death during treatment for TB. Up to 30% of such patients may die during treatment if no life prolonging ART is provided. The risk of death is higher in patients with smear negative disease and those with a lower CD 4 T cell count²²⁰. Life prolonging ART is able to dramatically reduce the deaths rates in HIV infected TB patients and the earlier it is given the better ²²¹. Cotrimoxazole preventive therapy is also able to reduce the mortality of HIV associated TB²²².

4.3.1.7 Prevention

HIV associated TB is a preventable disease. Several randomized clinical trials have demonstrated that TB can be effectively prevented using isoniazid given for 6-12 months in HIV infected persons²²³. With the advent of combined ART it was observed that TB incidence fell in persons on ART in North America and Europe. The fall in TB incidence has been observed to be greater in persons with a higher baseline CD4 T cell count, a lower base line viral load and robust immunological and virological responses²²⁴. Similar observations have been made in South Africa²²⁵. The combination of ART and Isoniazid Preventive Therapy (IPT) has been observed to confer greater protection against TB²²⁶ and provides further impetus to provide IPT in all HIV infected persons irrespective of whether they are or are not on ART. Currently there is no evidence that appropriately applied IPT leads to the expansion of isoniazid resistance²²⁷.

4.3.2 Other Mycobacteria

4.3.2.1 Mycobacterium Avium Complex and other Non Tuberculous Mycobacteria

Mycobacterium avium complex (MAC) is isolated with increasing frequency from respiratory specimens in HIV infected persons, however, the significance of isolating MAC from respiratory specimens is unclear. Criteria have been developed for defining clinical disease in patients who have non Tuberculous Mycobacteria isolated from respiratory samples²²⁸. HIV infected persons with pulmonary MAC are more likely to have fever, diffuse pulmonary abnormalities, lymphadenopathy and concurrent disease including disseminated MAC, PCP and BP compared with HIV negative individuals²²⁹. These infections generally occur late in the course of HIV disease and confer a poor long term prognosis²³⁰.

4.4 Viral pneumonia

Viral pathogens have also been implicated in HIV associated lung disease. These viruses have included Cytomegalovirus (CMV), Herpes Simplex Virus (HSV) and Influenza including H1N1. For CMV the difficulty has been distinguishing infection from colonization. The most important risk factor for viral pneumonia is a CD 4 T cell count below 200. These pneumonias may be difficult to diagnose and carry a high mortality.

4.4.1 CMV

This is the most common virus that has been implicated in HIV associated pneumonia. The clinical presentation is similar to pneumonia due to other pathogens and is largely non specific. The symptoms include fever, shortness of breath, and cough. Pneumonia due to CMV may be the initial presentation of HIV disease²³¹ and in the pre ART era, survival post CMV pneumonia, when successfully treated was short^{232, 233}. Often CMV pneumonia is not recognized or diagnosed prior to death^{234, 235}. Patients with a high plasma viral load may also be at risk of CMV pneumonia²³⁶.

The diagnosis of CMV may be problematic. When isolated in respiratory specimens such as bronchoalveolar lavage this virus may be a colonizer and not necessarily the cause of the lung disease²³⁷. To diagnose respiratory disease the current consensus is that CMV should be isolated in lung secretions (BAL or brushes), and demonstrated to be available in histological specimens through immunohistochemistry or in situ hybridization in the presence of pulmonary infiltrates on the chest radiograph. The treatment of CMV involves the use of ganciclovir or foscarnet.

As with fungal pneumonia the most important intervention for the prevention of CMV pneumonia is immune reconstitution using anti-retroviral treatment. No chemo preventive intervention has been identified. Acyclovir has been tried but was not found to be efficacious²³⁸

4.4.2 Herpes simplex

Herpes simplex virus type 1 and type 2 have both been associated with HIV pneumonia. The pneumonia may occur in association with cutaneous herpes and thus represent disseminated disease^{239, 240}. Varicella pneumonia has been described and may present as a recurrent pneumonia²⁴¹.

4.5 Parasitic lung disease in HIV

Lung disease caused by parasites may be less common. The most common parasites that have been associated with HIV lung disease are *Toxoplasma gondii* and *Strongyloides stercoralis*.

Epidemiological studies to obtain good estimates of the incidence of these parasites in HIV infected persons have not been carried out.

4.6 Non infectious HIV associated lung disease

Several non infectious lung diseases have been observed in HIV infected persons. These diseases include pulmonary arterial hypertension, bronchiolitis obliterans organizing pneumonia, sarcoidosis and chronic obstructive pulmonary disease. The incidence of these diseases may be increasing as HIV infected individuals survive longer with cART.

4.6.1 Interstitial pneumonitis

The HIV syndrome is associated with an increased incidence of non specific interstitial pneumonitis and lymphoid interstitial pneumonitis, both of which may result from the chronic inflammatory state induced by HIV^{242,243}. Lymphocytic Interstitial pneumonia in HIV infected persons may be associated with respiratory symptoms of cough and dyspnoea and cause lung function abnormalities²⁴⁴. The radiological picture is diffuse interstitial shadowing and a lung biopsy procedure is required for the diagnosis. The disease has been thought to be related to the host immune response²⁴⁵ and directly linked to HIV²⁴⁶. There is usually a predominance of CD8 positive T lymphocytes²²⁶. This entity may also occur as part of the immune reconstitution inflammatory syndrome²⁴⁷. It responds to systemic steroids and also resolves with ART^{248,249}. The incidence has declined with the widespread use of anti-retroviral treatment²⁵⁰

4.6.2 Non specific pneumonitis

A non specific pneumonitis associated with cough and dyspnoea and diffuse interstitial shadowing on the chest x-ray often occurs in HIV infected persons. This disease entity may mimic PcP²⁵¹ and even appear to respond to PcP treatment²⁵². However a search for *Pneumocystis jirovecii* is usually negative²⁵³.

4.6.3 Immune reconstitution inflammatory syndrome

The immune reconstitution inflammatory syndrome represents an exaggerated immune response to infectious and non infectious agents as immune recovery occurs. The syndrome is characterized by the appearance of worsening symptoms and signs of specific infections as immune recovery takes place. While most episodes are mild, severe life threatening disease may occur. The syndrome has been described to occur with many infections including *Pneumocystis jirovecii*, CMV, TB and *Cryptococcus*^{254,255,256,257}.

4.6.4 Pulmonary Arterial Hypertension (PAH)

Pulmonary arterial hypertension associated with HIV is a rare clinical entity but when it occurs it leads to significant morbidity and mortality. The available literature is mostly based on case reports. This clinical entity appears to occur at relatively high CD4 T cell of about 300. The clinical, radiographic and echocardiographic findings are similar to idiopathic PAH in HIV sero negative persons. Highly active antiretroviral therapy, bosentan, and prostaglandin therapy have all been reported to be beneficial in improving hemodynamic and functional status in HIV-related PAH²⁵⁸. In a French study the median survival of patients with HIV associated PAH receiving ART and PAH specific therapy was 88% and 72% at 1 and 3 years respectively. There was better survival in patients with CD4 T cell count of greater than 200 and a higher cardiac index. Anti-retroviral therapy did not appear to influence hemodynamic parameters²⁵⁹.

4.6.5 Pulmonary malignancies in HIV infected persons

Both Kaposi sarcoma (KS) and non Hodgkins Lymphoma (NHL), the two AIDS defining malignancies (ADMs) have been associated with lung disease. Of the two malignancies KS has been the more common one. In HIV associated KS, the tumour most often afflicts the lung as part of a disseminated disease process but may also occur as a primary lung disease. Non Hodgkins lymphoma occurring as primary lung disease has been described in several case reports and series⁵¹. Persons living with HIV appear to be at increased risk of primary lung cancer, a non ADM⁵².

Endobronchial Kaposi Sarcoma is seen in about 15% of patients with advanced HIV disease. The clinical presentation is indistinguishable from that of other pulmonary complications of HIV. Thus patients may present with cough, haemoptysis and dyspnoea. Both alveolar and interstitial shadows may be seen on the chest radiograph. Chest CT scans usually reveal the shadows better. The diagnosis requires visual detection of typical cherry red lesions at fiberoptic bronchoscopy. The lesions are usually not biopsied because of the risk of bleeding. Pulmonary KS usually occurs in the setting of disseminated KS and the prognosis is typically poor.

Non Hodgkins lymphoma involving the lung has been reported in case series and cohorts. The clinical presentation is usually non specific and includes fever, weight loss, dyspnea, generalized lymphadenopathy, chest pain and cough. The chest radiograph reveals nodular lesions or interstitial shadows. The diagnosis of lymphoma is more reliably made on open lung biopsy. In the pre - ART era the diagnosis of NHL carried with it a poor prognosis even with specific lymphoma treatment²⁶⁰.

The risk of lung cancer in HIV infected persons appears to be increased and this increase may not be fully explained by smoking²⁶¹. Although the data is scanty, recurrent pneumonia, through the promotion of chronic infection has been found to be associated with the increased risk of lung cancer in HIV infected persons²⁶². The incidence of lung cancer, may have increased in post HAART era²⁶³. However the incidence of lung cancer in HIV infected women appears not to be higher than that in HIV uninfected women and the driver of the lung cancer risk is tobacco smoking and not the HIV infection²⁶⁴. HIV infected patients with primary lung cancer are younger, tend to present with aggressive and advanced disease and have poorer outcomes^{265,266}.

4.6.6 Chronic obstructive pulmonary disease

Respiratory symptoms and functional abnormalities are common in patients infected with HIV including those on combined anti-retroviral therapy. A recent observational study documented respiratory symptoms and functional abnormalities in 47.3% and 64.1% of study participants respectively. Irreversible airways obstruction compatible with COPD, independently associated with pack years smoked, intravenous drug use and the use of anti-retroviral therapy was found in 21% of study participants²⁶⁷. In patients with obstructive airways disease, HIV infection appears to confer a higher risk of moderate but not severe dyspnoea²⁶⁸.

4.6.7 Bronchiolitis obliterans organizing pneumonia

Bronchiolitis obliterans organizing pneumonia (BOOP) is a disease of the small airways characterized by intraluminal polyps of myxoid connective tissue. The concomitant occurrence of BOOP with HIV has been described in a few case reports. In the cases reported, the clinical manifestations have included sub acute onset of dyspnoea which

progressed to respiratory failure, non productive cough and fever. The most common chest radiographic findings included bilateral mixed interstitial and alveolar shadows. When these patients are investigated for infection, no pathogens are found and empiric antibiotic therapy is not effective. The diagnosis of BOOP is made at open lung biopsy. Patients respond very well to corticosteroids at a dose of about 1 mg/Kg for up to three months²⁶⁹.

4.6.8 Hypersensitivity pneumonitis

Case reports of hypersensitivity pneumonitis associated with drugs used in the management of HIV infection including dapsone²⁷⁰, efavirenz²⁷¹ and other anti retrovirals²⁷² have been published. The burden of illness and or death caused hypersensitivity pneumonitis in HIV infected persons is currently unclear.

4.6.9 Sarcoidosis

Sarcoidosis is a multi system disease in which tissues are infiltrated with non caseating granulomas. The lung is a common target of sarcoid lesions. Pulmonary sarcoidosis associated with HIV has been reported in case reports and series^{273,274}. Many of the sarcoidosis case reports have appeared in the post HAART era and it is unclear if this entity, in the ART context is related to immune recovery. In patients who use adulterated drugs talc granulomatosis must be considered in the differential diagnosis of interstitial lung disease. This clinical entity is indistinguishable from opportunistic infections and requires examination of lung biopsy specimens which show granulomas with intracellular talc crystals²⁷⁵.

5. References

- [1] UNAIDS Report on the Global AIDS Epidemic 2010.
- [2] Masur H, Michelis MA, Greene JB, Onorato I, Stouwe RA, Holzman RS, Wormser G, Brettman L, Lange M, Murray HW, Cunningham-Rundles S. An outbreak of community-acquired *Pneumocystis carinii* pneumonia: initial manifestation of cellular immune dysfunction. *N Engl J Med*. 1981 Dec 10;305(24):1431-8.
- [3] Gottlieb MS, Schroff R, Schanker HM, Weisman JD, Fan PT, Wolf RA, Saxon A. *Pneumocystis carinii* pneumonia and mucosal candidiasis in previously healthy homosexual men: evidence of a new acquired cellular immunodeficiency. *N Engl J Med*. 1981 Dec 10;305(24):1425-31.
- [4] Centers for Disease Control (CDC). Kaposi's sarcoma and *Pneumocystis pneumonia* among homosexual men--New York City and California. *MMWR Morb Mortal Wkly Rep*. 1981 Jul 3;30(25):305-8.
- [5] Centers for Disease Control (CDC). A cluster of Kaposi's sarcoma and *Pneumocystis carinii* pneumonia among homosexual male residents of Los Angeles and Orange Counties, California. *MMWR Morb Mortal Wkly Rep*. 1982 Jun 18;31(23):305-7.)
- [6] Masur H, Michelis MA, Wormser GP, Lewin S, Gold J, Tapper ML, Giron J, Lerner CW, Armstrong D, Setia U, Sender JA, Siebken RS, Nicholas P, Arlen Z, Maayan S, Ernst JA, Siegal FP, Cunningham-Rundles S. Opportunistic infection in previously healthy women. Initial manifestations of a community-acquired cellular immunodeficiency. *Ann Intern Med*. 1982 Oct;97(4):533-9.

- [7] Design of a prospective study of the pulmonary complications of human immunodeficiency virus infection. The Pulmonary Complications of HIV Infection Study Group. *J Clin Epidemiol.* 1993 Jun;46(6):497-507
- [8] Diaz PT, Wewers MD, Pacht E, Drake J, Nagaraja HN, Clanton TL. Respiratory symptoms among HIV-seropositive individuals. *Chest.* 2003 Jun;123(6):1977-82
- [9] Buchacz K, Baker RK, Paella FJ Jr, Chmiel JS, Lichtenstein KA, Novak RM, Wood KC, Brooks JT; HOPS Investigators. AIDS-defining opportunistic illnesses in US patients, 1994-2007: a cohort study *AIDS.* 2010 Jun 19;24(10):1549-59
- [10] Hanna DB, Gupta LS, Jones LE, Thompson DM, Kellerman SE, Sackoff JE. AIDS-defining opportunistic illnesses in the HAART era in New York City. *AIDS Care.* 2007 Feb;19(2):264-72.
- [11] Bonnet F, Lewden C, May T, Heripret L, Jouglu E, Bevilacqua S, Costagliola D, Salmon D, Chêne G, Morlat P. Opportunistic infections as causes of death in HIV-infected patients in the HAART era in France.; Mortalité 2000 Study Group. *Scand J Infect Dis.* 2005;37(6-7):482-7
- [12] Crothers K, Huang L, Goulet JL, Goetz MB, Brown ST, Rodriguez-Barradas MC, Oursler KK, Rimland D, Gibert CL, Butt AA, Justice AC. HIV infection and risk for incident pulmonary diseases in the combination antiretroviral therapy era. *Am J Respir Crit Care Med.* 2011 Feb 1; 183(3):388-95. Epub 2010 Sep 17.
- [13] Bonnet F, Chêne G, Thiébaud R, Dupon M, Lawson-Ayayi S, Pellegrin JL, Dabis F, Morlat P; Groupe d'Epidémiologie Clinique du SIDA en Aquitaine (GECSA). Trends and determinants of severe morbidity in HIV-infected patients: the ANRS CO3 Aquitaine Cohort, 2000-2004. *HIV Med.* 2007 Nov;8(8):547-54.
- [14] Phair J, Muñoz A, Detels R, Kaslow R, Rinaldo C, Saah A. The risk of *Pneumocystis carinii* pneumonia among men infected with human immunodeficiency virus type 1. Multicenter AIDS Cohort Study Group. *N Engl J Med.* 1990 Jan 18;322(3):161-5.)
- [15] The Study on BV in HIV infected women in USA
- [16] Dufour V, Cadranet J, Wislez M, Lavole A, Bergot E, Parrot A, Rufat P, Mayaud C. Changes in the pattern of respiratory diseases necessitating hospitalization of HIV-infected patients since the advent of highly active antiretroviral therapy. *Lung.* 2004;182(6):331-41; 279.
- [17] Serraino D, Puro V, Boumis E, Angeletti C, Girardi E, Petrosillo N, Ippolito G. Epidemiological aspects of major opportunistic infections of the respiratory tract in persons with AIDS: Europe, 1993-2000. *AIDS.* 2003 Sep 26;17(14):2109-16;
- [18] Pulvirenti J, Herrera P, Venkataraman P, Ahmed N. *Pneumocystis carinii* pneumonia in HIV-infected patients in the HAART era. *AIDS Patient Care STDS.* 2003 Jun;17(6):261-5.
- [19] Grant AD, Sidibe K, Domoua K, et al. Spectrum of disease among HIV infected adults hospitalized in a respiratory medicine unit in Abidjan, Cote d'Ivoire. *Int J Tuberc Lung Dis* 1998; 2: 926-94
- [20] Dye C, Scheele S, Dolin P et al. Consensus statement: global burden of tuberculosis: estimated incidence, prevalence and mortality by country; WHO global surveillance and monitoring project. *JAMA* 1999; 228: 677-686
- [21] Range N, Ipuge YA, O'Brien RJ et al. Trend in HIV prevalence among tuberculosis patients in Tanzania, 1991-1998. *Int J Tuberc Lung Dis* 2001; 5: 405 -412
- [22] World Tuberculosis Report 2010, World Health Organization

- [23] Stringer JR, Cushion MT, Wakefield AE. New nomenclature for the genus *Pneumocystis*. *J. Eukaryot Microbiol* 2001; 48(suppl): 184 S-189S
- [24] Batungwanayo J, Taelman H, Lucas S, Bogaerts J, Alard D, Kagame A, Blanche P, Clerinx J, van de Perre P, Allen S. Pulmonary disease associated with the human immunodeficiency virus in Kigali, Rwanda. A fiberoptic bronchoscopic study of 111 cases of undetermined etiology. *Am J Respir Crit Care Med*. 1994 Jun;149(6):1591-6.
- [25] Lucas SB, Hounnou A, Peacock C, Beaumel A, Djomand G, N'Gbichi JM, Yeboue K, Hondé M, Diomande M, Giordano C, et al. The mortality and pathology of HIV infection in a west African city. *AIDS*. 1993 Dec;7(12):1569-79.
- [26] Atzori C, Bruno A, Chichino G, Gatti S, Scaglia M. *Pneumocystis carinii* pneumonia and tuberculosis in Tanzanian patients infected with HIV. *Trans R Soc Trop Med Hyg*. 1993 Jan-Feb;87(1):55-6.
- [27] Kamanfu G, Mlika-Cabanne N, Girard PM, Nimubona S, Mpfizi B, Cishako A, Roux P, Coulaud JP, Larouzé B, Aubry P, et al. Pulmonary complications of human immunodeficiency virus infection in Bujumbura, Burundi. *Am Rev Respir Dis*. 1993 Mar;147(3):658-63.
- [28] Lucas SB. Missing infections in AIDS. *Trans R Soc Trop Med Hyg* 1990; 84 Supl 1: 34 -8.
- [29] Chakaya JM, Bii C, Ng'ang'a L, Amukoye E, Ouko T, Muita L, Gathua S, Gitau J, Odongo I, Kabanga JM, Nagai K, Suzumura S, Sugiura Y. *Pneumocystis carinii* pneumonia in HIV/AIDS patients at an urban district hospital in Kenya. *East Afr Med J*. 2003 Jan;80(1):30-5.
- [30] Worodria W, Okot-Nwang M, Yoo SD, Aisu T. Causes of lower respiratory infection in HIV-infected Ugandan adults who are sputum AFB smear-negative. *Int J Tuberc Lung Dis*. 2003 Feb;7(2):117-23. 322.
- [31] Siika AM, Chakaya JM, Revathi G, Mohamed SS, Bhatt KM. Bronchoscopic study on aetiology of chronic cough in HIV-infected adults with negative sputum smears for *Mycobacterium tuberculosis* at Kenyatta National Hospital, Nairobi. *East Afr Med J*. 2006 Jun;83(6):295-305.; 321.
- [32] van Oosterhout JJ, Laufer MK, Perez MA, Graham SM, Chimbiya N, Thesing PC, Alvarez-Martinez MJ, Wilson PE, Chagomerana M, Zijlstra EE, Taylor TE, Plowe CV, Meshnick SR. *Pneumocystis pneumonia* in HIV-positive adults, Malawi. *Emerg Infect Dis*. 2007 Feb;13(2):325-8..
- [33] Lockman S, Hone N, Kenyon TA, Mwasekaga M, Villauthapillai M, Creek T, Zell E, Kirby A, Thacker WL, Talkington D, Moura IN, Binkin NJ, Clay L, Tappero JW. Etiology of pulmonary infections in predominantly HIV-infected adults with suspected tuberculosis, Botswana. *Int J Tuberc Lung Dis*. 2003 Aug;7(8):714-23
- [34] Garcia-Jardon M, Bhat VG, Blanco-Blanco E, Stepien A. Postmortem findings in HIV/AIDS patients in a tertiary care hospital in rural South Africa.. *Trop Doct*. 2010 Apr;40(2):81-4.
- [35] Nkinin SW, Daly KR, Walzer PD, Ndzi ES, Asonganyi T, Respaldiza N, Medrano FJ, Kaneshiro ES. Evidence for high prevalence of *Pneumocystis jirovecii* exposure among Cameroonians *Acta Trop*. 2009 Nov;112(2):219-24. Epub 2009 Aug 7.
- [36] Kaplan JE, Hanson DL, Navin TR, Jones JL. Risk factors for primary *Pneumocystis carinii* pneumonia in human immunodeficiency virus-infected adolescents and adults in the United States: reassessment of indications for chemoprophylaxis. *J Infect Dis*. 1998 Oct;178(4):1126-32.

- [37] Moorman AC, Von Bargen JC, Palella FJ, Holmberg SD. Pneumocystis carinii pneumonia incidence and chemoprophylaxis failure in ambulatory HIV-infected patients. HIV Outpatient Study (HOPS) Investigators. *J Acquir Immune Defic Syndr Hum Retrovirol.* 1998 Oct 1;19(2):182-8.
- [38] Stansell JD, Osmond DH, Charlebois E, LaVange L, Wallace JM, Alexander BV, Glassroth J, Kvale PA, Rosen MJ, Reichman LB, Turner JR, Hopewell PC. Predictors of Pneumocystis carinii pneumonia in HIV-infected persons. Pulmonary Complications of HIV Infection Study Group. *Am J Respir Crit Care Med.* 1997 Jan;155(1):60-6.
- [39] Richards PJ, Riddell L, Reznick RH, Armstrong P, Pinching AJ, Parkin JM. High resolution computed tomography in HIV patients with suspected Pneumocystis carinii pneumonia and a normal chest radiograph. *Clin Radiol.* 1996 Oct;51(10):689-93.
- [40] Moser E, Tatsch K, Kirsch CM, Küffer G, Goebel FD. Value of 67gallium scintigraphy in primary diagnosis and follow-up of opportunistic pneumonia in patients with AIDS. *Lung.* 1990;168 Suppl:692-703.
- [41] Chouaid C, Maillard D, Housset B, Febvre M, Zaoui D, Lebeau B. Cost effectiveness of noninvasive oxygen saturation measurement during exercise for the diagnosis of Pneumocystis carinii pneumonia. *Am Rev Respir Dis.* 1993 Jun;147(6 Pt 1):1360-3.
- [42] Stover DE, Greeno RA, Gagliardi AJ. The use of a simple exercise test for the diagnosis of Pneumocystis carinii pneumonia in patients with AIDS. *Am Rev Respir Dis.* 1989 Jun;139(6):1343-6.
- [43] Huang L, Stansell J, Osmond D, Turner J, Shafer KP, Fulkerson W, Kvale P, Wallace J, Rosen M, Glassroth J, Reichman L, Hopewell P. Performance of an algorithm to detect Pneumocystis carinii pneumonia in symptomatic HIV-infected persons. Pulmonary Complications of HIV Infection Study Group. *Chest.* 1999 Apr;115(4):1025-32.
- [44] Lewin SR, Hoy J, Crowe SM, McDonald CF. The role of bronchoscopy in the diagnosis and treatment of pulmonary disease in HIV-infected patients. *Aust N Z J Med.* 1995 Apr;25(2):133-9
- [45] Djamin RS, Drent M, Schreurs AJ, Groen EA, Wagenaar SS. Diagnosis of Pneumocystis carinii pneumonia in HIV-positive patients. Bronchoalveolar lavage versus bronchial brushing. *Acta Cytol.* 1998 Jul-Aug;42(4):933-8.
- [46] Morris A, Kingsley LA, Groner G, Lebedera IP, Beard CB, Norrisk A. Prevalence and clinical predictors of Pneumocystis colonization among HIV infected men. *AIDS* 2004; 18(5): 793-798
- [47] Aderaye G, Woldeamanuel Y, Asrat D, Lebbad M, Beser J, Worku A, Fernandez V, Lindquist L. Evaluation of Toluidine Blue O staining for the diagnosis of Pneumocystis jirovecii in expectorated sputum sample and bronchoalveolar lavage from HIV-infected patients in a tertiary care referral center in Ethiopia. *Infection.* 2008 Jun;36(3):237-43. Epub 2008 May 15.
- [48] Cruciani M, Marcati P, Malena M, Bosco O, Serpelloni G, Mengoli C. Meta-analysis of diagnostic procedures for Pneumocystis carinii pneumonia in HIV-1-infected patients. *Eur Respir J.* 2002 Oct;20(4):982-9.
- [49] Desmet S, Van Wijngaerden E, Maertens J, Verhaegen J, Verbeken E, De Munter P, Meersseman W, Van Meensel B, Van Eldere J, Lagrou K. Serum (1-3)-beta-D-glucan as a tool for diagnosis of Pneumocystis jirovecii pneumonia in patients with human

- immunodeficiency virus infection or hematological malignancy. *J Clin Microbiol.* 2009 Dec;47(12):3871-4. Epub 2009 Oct 21.
- [50] Watanabe T, Yasuoka A, Tanuma J, Yazaki H, Honda H, Tsukada K, Honda M, Gatanaga H, Teruya K, Kikuchi Y, Oka S. Serum (1 \rightarrow 3) beta-D-glucan as a noninvasive adjunct marker for the diagnosis of *Pneumocystis pneumonia* in patients with AIDS. *Clin Infect Dis.* 2009 Oct 1;49(7):1128-31.
- [51] Thomas M, Rupali P, Woodhouse A, Ellis-Pegler R. Good outcome with trimethoprim 10 mg/kg/day-sulfamethoxazole 50 mg/kg/day for *Pneumocystis jirovecii* pneumonia in HIV infected patients. *Scand J Infect Dis.* 2009;41(11-12):862-8.
- [52] Helweg-Larsen J, Benfield T, Atzori C, Miller RF. Clinical efficacy of first- and second-line treatments for HIV-associated *Pneumocystis jirovecii* pneumonia: a tri-centre cohort study. *J Antimicrob Chemother.* 2009 Dec;64(6):1282-90. Epub 2009 Oct 26
- [53] Short CE, Gilleece YC, Fisher MJ, Churchill DR. Trimetrexate and folinic acid: a valuable salvage option for *Pneumocystis jirovecii* pneumonia. *AIDS.* 2009 Jun 19;23(10):1287-90.
- [54] Smego RA Jr, Nagar S, Maloba B, Popara M. A meta-analysis of salvage therapy for *Pneumocystis carinii* pneumonia. *Arch Intern Med.* 2001 Jun 25;161(12):1529-33.)
- [55] Fei MW, Kim EJ, Sant CA, Jarlsberg LG, Davis JL, Swartzman A, Huang L. Predicting mortality from HIV-associated *Pneumocystis pneumonia* at illness presentation: an observational cohort study. *Thorax.* 2009 Dec;64(12):1070-6. Epub 2009 Oct 12.
- [56] Walzer PD, Evans HE, Copas AJ, Edwards SG, Grant AD, Miller RF. Early predictors of mortality from *Pneumocystis jirovecii* pneumonia in HIV-infected patients: 1985-2006. *Int J STD AIDS.* 2009 Sep;20(9):652-3.
- [57] Fisk M, Sage EK, Edwards SG, Cartledge JD, Miller RF. Outcome from treatment of *Pneumocystis jirovecii* pneumonia with co-trimoxazole. *Clin Infect Dis.* 2008 Feb 15;46(4):625-33
- [58] Bédos JP, Dumoulin JL, Gachot B, Veber B, Wolff M, Régnier B, Chevret S. *Pneumocystis carinii* pneumonia requiring intensive care management: survival and prognostic study in 110 patients with human immunodeficiency virus. *Crit Care Med.* 1999 Jun;27(6):1109-15.
- [59] Boonsarnsuk V, Sirilak S, Kiatboonsri S. Acute respiratory failure due to *Pneumocystis pneumonia*: outcome and prognostic factors. *Int J Infect Dis.* 2009 Jan;13(1):59-66. Epub 2008 Jun 24
- [60] Forrest DM, Zala C, Djurdjev O, Singer J, Craib KJ, Lawson L, Russell JA, Montaner JS. Determinants of short- and long-term outcome in patients with respiratory failure caused by AIDS-related *Pneumocystis carinii* pneumonia. *Arch Intern Med.* 1999 Apr 12;159(7):741-7
- [61] National Institutes of Health - University of California Expert panel for corticosteroids as adjunctive therapy for *Pneumocystis pneumonia* in the acquired immunodeficiency syndrome. *N Eng J med* 1990; 323: 1500-1504
- [62] Bozette SA, Sattler FR, Chiu J et al. A controlled trial of early adjunctive treatment with corticosteroids for *Pneumocystis carinii* pneumonia in the acquired immunodeficiency syndrome. *N Eng J Med* 1990; 323: 1441 -1457
- [63] Gagnon S, Boota AM, Fischl MA et al. Corticosteroids as adjunctive therapy for severe *Pneumocystis pneumonia* in the acquired immunodeficiency syndrome: a double blind placebo controlled trial. *N Eng J Med* 1990; 1990: 1444-1450

- [64] Montaner JSG, Lawson LM, Levitt N et al. Corticosteroids prevent early deterioration in patients with moderately severe *Pneumocystis carinii* pneumonia and the acquired immunodeficiency syndrome (AIDS). *Ann Intern Med* 1990; 113: 14-20
- [65] Gallant JE, Chaisson RE, Moore RD. The effect of adjunctive corticosteroids for the treatment of *Pneumocystis carinii* pneumonia on mortality and subsequent complications. *Chest*. 1998 Nov;114(5):1258-63.
- [66] Walmsley S, Levinton C, Brunton J, Muradali D, Rappaport D, Bast M, Spence D, Salit I. A multicenter randomized double-blind placebo-controlled trial of adjunctive corticosteroids in the treatment of *Pneumocystis carinii* pneumonia complicating the acquired immune deficiency syndrome. *J Acquir Immune Defic Syndr Hum Retrovirol*. 1995 Apr 1;8(4):348-57.
- [67] Crothers K, Beard CB, Turner J, Groner G, Fox M, Morris A, Eiser S, Huang L. Severity and outcome of HIV-associated *Pneumocystis* pneumonia containing *Pneumocystis jirovecii* dihydropteroate synthase gene mutations. *AIDS*. 2005 May 20;19(8):801-5.
- [68] Navin TR, Beard CB, Huang L, del Rio C, Lee S, Pieniazek NJ, Carter JL, Le T, Hightower A, Rimland D. Effect of mutations in *Pneumocystis carinii* dihydropteroate synthase gene on outcome of *P. carinii* pneumonia in patients with HIV-1: a prospective study. *Lancet*. 2001 Aug 18;358(9281):545-9.
- [69] Helweg-Larsen J, Benfield TL, Eugen-Olsen J, Lundgren JD, Lundgren B. Effects of mutations in *Pneumocystis carinii* dihydropteroate synthase gene on outcome of AIDS-associated *P. carinii* pneumonia. *Lancet*. 1999 Oct 16;354(9187):1347-51.
- [70] Sage EK, Noursadeghi M, Evans HE, Parker SJ, Copas AJ, Edwards SG, Miller RF. Prognostic value of C-reactive protein in HIV-infected patients with *Pneumocystis jirovecii* pneumonia. *Int J STD AIDS*. 2010 Apr;21(4):288-92.
- [71] Rizzardi GP, Lazzarin A, Musicco M, Frigerio D, Maillard M, Lucchini M, Moroni M. Risks and benefits of aerosolized pentamidine and cotrimoxazole in primary prophylaxis of *Pneumocystis carinii* pneumonia in HIV-1-infected patients: a two-year Italian multicentric randomized controlled trial. The Italian PCP Study Group. *J Infect*. 1996 Mar;32(2):123-31
- [72] Warnock AC, Rimland D. Comparison of trimethoprim-sulfamethoxazole, dapsone, and pentamidine in the prophylaxis of *Pneumocystis carinii* pneumonia. *Pharmacotherapy*. 1996 Nov-Dec;16(6):1030-8.
- [73] Chan C, Montaner J, Lefebvre EA, Morey G, Dohn M, McIvor RA, Scott J, Marina R, Caldwell P. Atovaquone suspension compared with aerosolized pentamidine for prevention of *Pneumocystis carinii* pneumonia in human immunodeficiency virus-infected subjects intolerant of trimethoprim or sulfonamides. *J Infect Dis*. 1999 Aug;180(2):369-76.
- [74] Kazanjian P, Locke AB, Hossler PA, Lane BR, Bartlett MS, Smith JW, Cannon M, Meshnick SR. *Pneumocystis carinii* mutations associated with sulfa and sulfone prophylaxis failures in AIDS patients. *AIDS*. 1998 May 28;12(8):873-8
- [75] Nahimana A, Rabodonirina M, Bille J, Francioli P, Hauser PM. Mutations of *Pneumocystis jirovecii* dihydrofolate reductase associated with failure of prophylaxis. *Antimicrob Agents Chemother*. 2004 Nov;48(11):4301-5.
- [76] El-Sadr WM, Murphy RL, Yurik TM, Luskin-Hawk R, Cheung TW, Balfour HH Jr, Eng R, Hooton TM, Kerkering TM, Schutz M, van der Horst C, Hafner R. Atovaquone compared with dapsone for the prevention of *Pneumocystis carinii* pneumonia in patients with HIV infection who cannot tolerate trimethoprim, sulfonamides, or

- both. Community Program for Clinical Research on AIDS and the AIDS Clinical Trials Group. *N Engl J Med.* 1998 Dec 24;339(26):1889-95.
- [77] Lopez Bernaldo de Quiros JC, Miro JM, Peña JM, Podzamczar D, Alberdi JC, Martínez E, Cosin J, Claramonte X, Gonzalez J, Domingo P, Casado JL, Ribera E; Grupo de Estudio del SIDA 04/98. A randomized trial of the discontinuation of primary and secondary prophylaxis against *Pneumocystis carinii* pneumonia after highly active antiretroviral therapy in patients with HIV infection. *Grupo de Estudio del SIDA 04/98. N Engl J Med.* 2001 Jan 18;344(3):159-67.
- [78] Cheng CY, Chen MY, Hsieh SM, Sheng WH, Sun HY, Lo YC, Liu WC, Hung CC. May 21;10:126. Risk of pneumocystosis after early discontinuation of prophylaxis among HIV-infected patients receiving highly active antiretroviral therapy. *BMC Infect Dis.* 2010
- [79] D'Egidio GE, Kravcik S, Cooper CL, Cameron DW, Fergusson DA, Angel JB. *Pneumocystis jirovecii* pneumonia prophylaxis is not required with a CD4+ T-cell count < 200 cells/microl when viral replication is suppressed. *AIDS.* 2007 Aug 20;21(13):1711-5.
- [80] Scourfield A, Tan LK, Nelson M. Severe septic-shock like reaction to co-trimoxazole in an HIV-positive man *Int J STD AIDS.* 2010 Jul;21(7):521-3.
- [81] Cho JY, Kim DM, Kwon YE, Yoon SH, Lee SI Newly formed cystic lesions for the development of pneumomediastinum in *Pneumocystis jirovecii* pneumonia *BMC Infect Dis.* 2009 Oct 18;9:171.
- [82] Batungwanayo J, Taelman H, Bogaerts J, Allen S, Lucas S, Kagame A, Clerinx J, Montané J, Saraux A, Mühlberger F, et al. Pulmonary cryptococcosis associated with HIV-1 infection in Rwanda: a retrospective study of 37 cases. *AIDS.* 1994 Sep;8(9):1271-6.
- [83] Lee KH, Chang UI, Kim HW, Kim G, Kim SK, Yoo J, Wie SH. Acute respiratory failure associated with cryptococcal pneumonia and disseminated cryptococcosis in an AIDS patient *Korean J Intern Med.* 2006 Mar;21(1):39-42
- [84] Baddley JW, Perfect JR, Oster RA, Larsen RA, Pankey GA, Henderson H, Haas DW, Kauffman CA, Patel R, Zaas AK, Pappas PG. Pulmonary cryptococcosis in patients without HIV infection: factors associated with disseminated disease. *Eur J Clin Microbiol Infect Dis.* 2008 Oct;27(10):937-43. Epub 2008 May 1.
- [85] Denning DW, Follansbee SE, Scolaro M, Norris S, Edelstein H, Stevens DA. Pulmonary aspergillosis in the acquired immunodeficiency syndrome. *N Engl J Med.* 1991 Mar 7;324(10):654-62.
- [86] Klapholz A, Salomon N, Perlman DC, Talavera W. Aspergillosis in the acquired immunodeficiency syndrome. *Chest.* 1991 Dec;100(6):1614-8.
- [87] Klapholz A, Salomon N, Perlman DC, Talavera W. Aspergillosis in the acquired immunodeficiency syndrome. *Chest.* 1991 Dec;100(6):1614-8.
- [88] Vathesatogkit P, Goldenberg R, Parsey M. A 27-year-old HIV-infected woman with severe sepsis and pulmonary infiltrates. Disseminated histoplasmosis with severe sepsis and acute respiratory failure. *Chest.* 2003 Jan;123(1):272-3, 274-6.
- [89] Mora DJ, dos Santos CT, Silva-Vergara ML. Disseminated histoplasmosis in acquired immunodeficiency syndrome patients in Uberaba, MG, Brazil. *Mycoses.* 2008 Mar;51(2):136-40.

- [90] Pappas PG, Pottage JC, Powderly WG, Fraser VJ, Stratton CW, McKenzie S, Tapper ML, Chmel H, Bonebrake FC, Blum R, et al. Blastomycosis in patients with the acquired immunodeficiency syndrome *Ann Intern Med.* 1992 May 15;116(10):847-53.
- [91] Limper AH, Knox KS, Sarosi GA, Ampel NM, Bennett JE, Catanzaro A, Davies SF, Dismukes WE, Hage CA, Marr KA, Mody CH, Perfect JR, Stevens DA; American Thoracic Society Fungal Working Group. An official american thoracic society statement: treatment of fungal infections in adult pulmonary and critical care patients. *Am J Respir Crit Care Med.* 2011 Jan 1;183(1):96-128
- [92] Charalambous S, Day JH, Fielding K, De Cock KM, Churchyard GJ, Corbett EL. HIV infection and chronic chest disease as risk factors for bacterial pneumonia: a case-control study. *AIDS.* 2003 Jul 4;17(10):1531-7.
- [93] Falguera M, Martín M, Ruiz-González A, Pifarré R, García M. Community-acquired pneumonia as the initial manifestation of serious underlying diseases. *Am J Med.* 2005 Apr;118(4):378-83.
- [94] Inverarity D, Bradshaw Q, Wright P, Grant A. The spectrum of HIV-related disease in rural Central Thailand. *Southeast Asian J Trop Med Public Health.* 2002 Dec;33(4):822-31
- [95] Sullivan JH, Moore RD, Keruly JC, Chaisson RE. Effect of antiretroviral therapy on the incidence of bacterial pneumonia in patients with advanced HIV infection *Am J Respir Crit Care Med.* 2000 Jul;162(1):64-7
- [96] Madeddu G, Porqueddu EM, Cambosu F, Saba F, Fois AG, Pirina P, Mura MS. Bacterial community acquired pneumonia in HIV-infected inpatients in the highly active antiretroviral therapy era. *Infection.* 2008 Jun;36(3):231-6. Epub 2008 May 10.
- [97] Saindou M, Chidiac C, Miaillhes P, Voirin N, Baratin D, Amiri M, Livrozet JM, Touraine JL, Trepo C, Peyramond D, Vanhems P. Pneumococcal pneumonia in HIV-infected patients by antiretroviral therapy periods *HIV Med.* 2008 Apr;9(4):203-7. Epub 2008 Feb 21
- [98] Barbier F, Coquet I, Legriel S, Pavie J, Darmon M, Mayaux J, Molina JM, Schlemmer B, Azoulay E. Etiologies and outcome of acute respiratory failure in HIV-infected patients *Intensive Care Med.* 2009 Oct;35(10):1678-86. Epub 2009 Jul 3
- [99] Soeiro Ade M, Hovnanian AL, Parra ER, Canzian M, Capelozzi VL. Post-mortem histological pulmonary analysis in patients with HIV/AIDS. *Clinics (Sao Paulo).* 2008 Aug;63(4):497-502.
- [100] Martinson NA, Karstaedt A, Venter WD, Omar T, King P, Mbengo T, Marais E, McIntyre J, Chaisson RE, Hale M. Causes of death in hospitalized adults with a premortem diagnosis of tuberculosis: an autopsy study *AIDS.* 2007 Oct 1;21(15):2043-50.
- [101] Wallace JM, Hansen NI, Lavange L, Glassroth J, Browdy BL, Rosen MJ, Kvale PA, Mangura BT, Reichman LB, Hopewell PC. Pulmonary Complications of HIV Infection Study Group. Respiratory disease trends in the Pulmonary Complications of HIV Infection Study cohort. *Am J Respir Crit Care Med.* 1997 Jan;155(1):72-80.
- [102] Burns DN, Hillman D, Neaton JD, Sherer R, Mitchell T, Capps L, Vallier WG, Thurnherr MD, Gordin FM. Cigarette smoking, bacterial pneumonia, and other clinical outcomes in HIV-1 infection. Terry Bein Community Programs for Clinical Research on AIDS. *J Acquir Immune Defic Syndr Hum Retrovirol.* 1996 Dec 1;13(4):374-83.

- [103] Tumbarello M, Tacconelli E, de Gaetano K, Ardito F, Pirroni T, Cauda R, Ortona L. Bacterial pneumonia in HIV-infected patients: analysis of risk factors and prognostic indicators. *J Acquir Immune Defic Syndr Hum Retrovirol.* 1998 May 1;18(1):39-45.
- [104] Bénard A, Mercié P, Alioum A, Bonnet F, Lazaro E, Dupon M, Neau D, Dabis F, Chêne G; Groupe d'Epidémiologie Clinique du Sida en Aquitaine. Bacterial pneumonia among HIV-infected patients: decreased risk after tobacco smoking cessation. ANRS CO3 Aquitaine Cohort, 2000-2007. *PLoS One.* 2010 Jan 26;5(1):e8896
- [105] Gordin FM, Roediger MP, Girard PM, Lundgren JD, Miro JM, Palfreeman A, Rodriguez-Barradas MC, Wolff MJ, Easterbrook PJ, Clezy K, Slater LN. Pneumonia in HIV-infected persons: increased risk with cigarette smoking and treatment interruption. *Am J Respir Crit Care Med.* 2008 Sep 15;178(6):630-6. Epub 2008 Jul 10
- [106] Crothers K, Griffith TA, McGinnis KA, Rodriguez-Barradas MC, Leaf DA, Weissman S, Gibert CL, Butt AA, Justice AC. The impact of cigarette smoking on mortality, quality of life, and comorbid illness among HIV-positive veterans. *Intern Med.* 2005 Dec;20(12):1142-5.
- [107] Saindou M, Chidiac C, Miaillhes P, Voirin N, Baratin D, Amiri M, Livrozet JM, Touraine JL, Trepo C, Peyramond D, Vanhems P. Pneumococcal pneumonia in HIV-infected patients by antiretroviral therapy periods. *HIV Med.* 2008 Apr;9(4):203-7. Epub 2008 Feb 21
- [108] Moore RD, Keruly JC, Chaisson RE. Neutropenia and bacterial infection in acquired immunodeficiency syndrome. *Arch Intern Med.* 1995 Oct 9;155(18):1965-70.
- [109] Franzetti F, Grassini A, Piazza M, Degl'innocenti M, Bandera A, Gazzola L, Marchetti G, Gori A. Nosocomial bacterial pneumonia in HIV-infected patients: risk factors for adverse outcome and implications for rational empiric antibiotic therapy. *Infection.* 2006 Feb;34(1):9-16.
- [110] Tumbarello M, Tacconelli E, de Gaetano Donati K, Bertagnolio S, Cataldo M, Pirroni T, Ardito F, Cauda R. Nosocomial bacterial pneumonia in human immunodeficiency virus infected subjects: incidence, risk factors and outcome *Eur Respir J.* 2001 Apr;17(4):636-40.
- [111] Chave JP, Bille J, Glauser MP, Francioli P. Diagnosis of pulmonary infections in patients infected with the human immunodeficiency virus. *Eur J Clin Microbiol Infect Dis.* 1989 Feb;8(2):123-6.
- [112] French N, Williams G, Williamson V, Bhatt SM, Gilks CF. The radiographic appearance of pneumococcal pneumonia in adults is unaltered by HIV-1-infection in hospitalized Kenyans. *Br J Radiol.* 2007 May;80(953):302-6. Epub 2006 Sep 27
- [113] Rizzi EB, Schininá V, Rovighi L, Cristofaro M, Bordi E, Narciso P, Bibbolino C. HIV-related pneumococcal lung disease: does highly active antiretroviral therapy or bacteremia modify radiologic appearance? *AIDS Patient Care STDS.* 2008 Feb;22(2):105-11.
- [114] Shah RM, Gupta S, Angeid-Backman E, O'Donnell J. Pneumococcal pneumonia in patients requiring hospitalization: effects of bacteremia and HIV seropositivity on radiographic appearance. *AJR Am J Roentgenol.* 2000 Dec;175(6):1533-6.
- [115] Nyamande K, Lalloo UG, Vawda F. Comparison of plain chest radiography and high-resolution CT in human immunodeficiency virus infected patients with community-acquired pneumonia: a sub-Saharan Africa study. *AIDS.* 2002 Oct 18;16(15):2095-6

- [116] Mark PE. The clinical features of severe community acquired pneumonitis presenting as septic shock. Norasept II study investigators. *J. Crit Care* 2000; 15: 85-90
- [117] JAG Scott, AJ Hall, C Muyodi et al. Aetiology, outcome and risk factors for mortality among adults with acute pneumonia in Kenya. *Lancet* 200; 355(9211): 1225-1230
- [118] Watanakunakorn C, Bailey TA. Adult bacteremic pneumococcal pneumonia in a community teaching hospital 1992-1996: a detailed analysis of 108 cases. *Arch. Intern Med* 1997; 157: 1965-71
- [119] Storgaard M, Laursen AL, Andersen PL. The C-reactive protein responses in HIV-infected patients with pneumonia. *Scand J Infect Dis.* 1993;25(3):305-9.
- [120] Schleicher GK, Herbert V, Brink A, Martin S, Maraj R, Galpin JS, Feldman C. Procalcitonin and C-reactive protein levels in HIV-positive subjects with tuberculosis and pneumonia. *Eur Respir J.* 2005 Apr;25(4):688-92.
- [121] Lim WS, Vander Eerden MM, Laing R et al. Defining community acquired pneumonia severity on presentation to hospital. An international derivation and validation study. *Thorax* 2003; 58: 377-82
- [122] Fine MJ, Auble TE, Yealy DM et al. A prediction rule to identify low risk patients with community acquired pneumonia. *N. Eng J Med* 1997; 336: 243-50
- [123] Murray PR, Washington JA. Microscopic and bacteriologic analysis of expectorated sputum. *Mayo Clin Proc* 1975; 50(6): 339-44.
- [124] Boulware DR, Daley CL, Merrifield C, Hopewell PC, Janoff EN. Rapid diagnosis of pneumococcal pneumonia among HIV-infected adults with urine antigen detection *J Infect.* 2007 Oct;55(4):300-9. Epub 2007 Aug 10.
- [125] Cordero E, Pachón J, Rivero A, Girón-González JA, Gómez-Mateos J, Merino MD, Torres-Tortosa M, González-Serrano M, Aliaga L, Collado A, Hernández-Quero J, Barrera A, Nuño E Usefulness of sputum culture for diagnosis of bacterial pneumonia in HIV-infected patients. *Eur J Clin Microbiol Infect Dis.* 2002 May;21(5):362-7. Epub 2002 May 7.
- [126] da Silva RM, Teixeira PJ, Moreira Jda S. The clinical utility of induced sputum for the diagnosis of bacterial community-acquired pneumonia in HIV-infected patients: a prospective cross-sectional study. *Braz J Infect Dis.* 2006 Apr;10(2):89-93.
- [127] Daley CL, Mugusi F, Chen LL, Schmidt DM, Small PM, Bearer E, Aris E, Mtoni IM, Cegielski JP, Lallinger G, Mbaga I, Murray JF. Pulmonary complications of HIV infection in Dar es Salaam, Tanzania. Role of bronchoscopy and bronchoalveolar lavage. *Am J Respir Crit Care Med.* 1996 Jul;154(1):105-10.
- [128] Marcos MA, Jiménez de Anta MT, de la Bellacasa JP, González J, Martínez E, García E, Mensa J, de Roux A, Torres A. Rapid urinary antigen test for diagnosis of pneumococcal community-acquired pneumonia in adults. *Eur Respir J.* 2003 Feb;21(2):209-14.
- [129] Yzerman EP, den Boer JW, Lettinga KD, Schellekens J, Dankert J, Peeters M. Sensitivity of three urinary antigen tests associated with clinical severity in large outbreak of legionnaires disease in the Netherlands. *J clin Microbiol* 2002; 40: 3232-6
- [130] Shankar EM, Kumarasamy N, Balakrishnan P, Solomon S, Lejith R, Vengatesan A, Anand Rao U. Serosurveillance of acute *Mycoplasma pneumoniae* infection among HIV infected patients with pulmonary complaints in Chennai, Southern India. *J Infect.* 2006 Nov;53(5):325-30. Epub 2006 Jan 25.
- [131] Jiménez ML, Aspa J, Padilla B, Ancochea J, González A, Fraga J, Santos I, Martínez R, Gómez Herruz P, López-Brea M. Fiberoptic bronchoscopic diagnosis of pulmonary

- disease in 151 HIV-infected patients with pneumonitis. *Eur J Clin Microbiol Infect Dis.* 1991 Jun;10(6):491-6.
- [132] Heurlin N, Brattström C, Lönnqvist B, Westman L, Lidman C, Andersson J Aetiology of pulmonary diseases in immunocompromised patients. *Eur Respir J.* 1991 Jan;4(1):10-8.
- [133] Taylor IK, Coker RJ, Clarke J, Moss FM, Nieman R, Evans DJ, Veale D, Shaw RJ, Robinson DS, Mitchell DM. Pulmonary complications of HIV disease: 10 year retrospective evaluation of yields from bronchoalveolar lavage, 1983-93. *Thorax.* 1995 Dec;50(12):1240-5.
- [134] Daley CL, Mugusi F, Chen LL, Schmidt DM, Small PM, Bearer E, Aris E, Mtoni IM, Cegielski JP, Lallinger G, Mbaga I, Murray JF. Pulmonary complications of HIV infection in Dar es Salaam, Tanzania. Role of bronchoscopy and bronchoalveolar lavage *Am J Respir Crit Care Med.* 1996 Jul;154(1):105-10.
- [135] Falguera M, Nogues A, Ruiz-González A, García M, Puig T, Rubio-Caballero M. Transthoracic needle aspiration in the study of pulmonary infections in patients with HIV. *Chest.* 1994 Sep;106(3):697-702.
- [136] McLeod DT, Neill P, Robertson VJ, Latif AS, Emmanuel JC, Els JE, Gwanzura LK, Trijssenaar FE, Nziramasanga P, Jongeling GR, et al. Pulmonary diseases in patients infected with the human immunodeficiency virus in Zimbabwe, Central Africa. *Trans R Soc Trop Med Hyg.* 1989 Sep-Oct;83(5):694-7.
- [137] Jensen BN, Gerstoft J, Højlyng N, Backer V, Paaske M, Gomme G, Skinhøj P. Pulmonary pathogens in HIV-infected patients. *Scand J Infect Dis.* 1990;22(4):413-20.
- [138] McLoughlin P, Mulcahy F, O'Briain DS, Kane B, Mulvihill E, Prichard JS. Lung pathology in HIV positive patients. *Ir Med J.* 1990 Sep;83(3):109-11.
- [139] Redd SC, Rutherford GW 3rd, Sande MA, Lifson AR, Hadley WK, Facklam RR, Spika JS. The role of human immunodeficiency virus infection in pneumococcal bacteremia in San Francisco residents. *J Infect Dis.* 1990 Nov;162(5):1012-7.
- [140] Feldman C, Glatthaar M, Morar R, Mahomed AG, Kaka S, Cassel M, Klugman KP. Bacteremic pneumococcal pneumonia in HIV-seropositive and HIV-seronegative adults. *Chest.* 1999 Jul;116(1):107-14.
- [141] Koulla-Shiro S, Kuaban C, Belec L. Acute community-acquired bacterial pneumonia in Human Immunodeficiency Virus (HIV) infected and non-HIV-infected adult patients in Cameroon: aetiology and outcome. *Tuber Lung Dis.* 1996 Feb;77(1):47-51.
- [142] Pesola GR, Charles A. Pneumococcal bacteremia with pneumonia. Mortality in acquired immunodeficiency syndrome. *Chest.* 1992 Jan;101(1):150-5.
- [143] Falcó V, Fernández de Sevilla T, Alegre J, Barbé J, Ferrer A, Ocaña I, Ribera E, Martínez-Vázquez JM. Bacterial pneumonia in HIV-infected patients: a prospective study of 68 episodes. *Eur Respir J.* 1994 Feb;7(2):235-9.
- [144] Topino S, Galati V, Grilli E, Petrosillo N Rhodococcus equi infection in HIV-infected individuals: case reports and review of the literature. *AIDS Patient Care STDS.* 2010 Apr;24(4):211-22
- [145] Hulsewé-Evers HP, Jansveld CA, Jansz AR, Schneider MM, Bravenboer B. HIV-infected patient with a Rhodococcus equi pneumonia. *Neth J Med.* 2000 Jul;57(1):25-9.
- [146] Frame BC, Petkus AF. Rhodococcus equi pneumonia: case report and literature review. *Ann Pharmacother.* 1993 Nov;27(11):1340-2

- [147] Vanschooneveld T, Mindru C, Madariaga MG, Kalil AC, Florescu DF. Enterococcus pneumonia complicated with empyema and lung abscess in an HIV-positive patient. Case report and review of the literature. *Int J STD AIDS*. 2009 Sep;20(9):659-6
- [148] Unkle DW, Ricketti AJ, Cleri DJ, Moser RL, Vernaleo JR. An HIV-infected patient with *Nocardia asteroides* bilateral pneumonia. *AIDS Read*. 2008 Nov;18(11):566-8.
- [149] Menéndez R, Cordero PJ, Santos M, Gobernado M, Marco V. Pulmonary infection with *Nocardia* species: a report of 10 cases and review. *Eur Respir J*. 1997 Jul;10(7):1542-6.
- [150] Sandkovsky U, Sandkovsky G, Suh J, Smith B, Sharp V, Polsky B. Legionella pneumonia and HIV: case reports and review of the literature. *AIDS Patient Care STDS*. 2008 Jun;22(6):473-81.
- [151] Bangsberg JM, Jensen BN, Friis-Møller A, Bruun B. Legionellosis in patients with HIV infection. *Infection*. 1990 Nov-Dec;18(6):342-6.
- [152] Shankar EM, Kumarasamy N, Vignesh R, Balakrishnan P, Solomon SS, Murugavel KG, Saravanan S, Velu V, Farooq SM, Hayath K, Muthu S, Solomon S, Rao UA. Epidemiological studies on pulmonary pathogens in HIV-positive and -negative subjects with or without community-acquired pneumonia with special emphasis on *Mycoplasma pneumoniae*. *Jpn J Infect Dis*. 2007 Nov;60(6):337-41.
- [153] Lockman S, Hone N, Kenyon TA, Mwasekaga M, Villauthapillai M, Creek T, Zell E, Kirby A, Thacker WL, Talkington D, Moura IN, Binkin NJ, Clay L, Tappero JW. Etiology of pulmonary infections in predominantly HIV-infected adults with suspected tuberculosis, Botswana. *Int J Tuberc Lung Dis*. 2003 Aug;7(8):714-23
- [154] Manfredi R, Nanetti A, Valentini R, Chiodo F. *Moraxella catarrhalis* pneumonia during HIV disease. *J Chemother*. 2000 Oct;12(5):406-11.
- [155] Schuster MG, Norris AH Community-acquired *Pseudomonas aeruginosa* pneumonia in patients with HIV infection. *AIDS*. 1994 Oct;8(10):1437-41.
- [156] Ali NJ, Kessel D, Miller RF Bronchopulmonary infection with *Pseudomonas aeruginosa* in patients infected with human immunodeficiency virus. *Genitourin Med*. 1995 Apr;71(2):73-7.
- [157] Dropulic LK, Leslie JM, Eldred LJ, Zenilman J, Sears CL Clinical manifestations and risk factors of *Pseudomonas aeruginosa* infection in patients with AIDS. *J Infect Dis*. 1995 Apr;171(4):930-7.
- [158] Casado JL, Navas E, Frutos B, Moreno A, Martín P, Hermida JM, Guerrero A. *Salmonella* lung involvement in patients with HIV infection. *Chest*. 1997 Nov 5;112(5):1197-201.
- [159] Watanabe H, Asoh N, Kobayashi S, Watanabe K, Oishi K, Kositsakulchai W, Sanchai T, Khantawa B, Tharavichitkul P, Sirisanthana T, Nagatake T. Clinical and microbiological characteristics of community-acquired pneumonia among human immunodeficiency virus-infected patients in northern Thailand. *J Infect Chemother*. 2008 Apr;14(2):105-9. Epub 2008 Apr 30
- [160] Vray M, Germani Y, Chan S, Duc NH, Sar B, Sarr FD, Bercion R, Rahalison L, Maynard M, L'Her P, Chartier L, Mayaud C. Clinical features and etiology of pneumonia in acid-fast bacillus sputum smear-negative HIV-infected patients hospitalized in Asia and Africa. *AIDS*. 2008 Jul 11;22(11):1323-32.
- [161] Castro JG, Manzi G, Espinoza L, Campos M, Boulanger C. Concurrent PCP and TB pneumonia in HIV infected patients. *Scand J Infect Dis*. 2007;39(11-12):1054-8. Epub 2007 Jun 21.

- [162] Soubani AO, Ibrahim I, Forlenza S. Simultaneous nocardial empyema and *Pneumocystis carinii* pneumonia as an initial manifestation of HIV infection. *South Med J*. 1993 Nov;86(11):1318-9.
- [163] Aspa J, Rajas O, Rodriguez de Castro F, Huertas MC, Borderías L, Cabello FJ, Tábara J, Hernández-Flix S, Martínez-Sanchis A, Torres A; Pneumococcal Pneumonia in Spain Study Group. Impact of initial antibiotic choice on mortality from pneumococcal pneumonia. *Eur Respir J*. 2006 May;27(5):1010-9. Epub 2006 Feb 2.
- [164] Mandell CA, Wunderink RG, Anzueto A et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community acquired pneumonia in adults. *Clin Infect Dis* 2007; 44(Suppl 2): S27-72
- [165] Gwanzura L, Pasi C, Nathoo KJ, Hakim J, Gangaidzo I, Mielke J, Robertson VJ, Heyderman RS, Mason PR. Rapid emergence of resistance to penicillin and trimethoprim-sulphamethoxazole in invasive *Streptococcus pneumoniae* in Zimbabwe. *Int J Antimicrob Agents*. 2003 Jun;21(6):557-61.
- [166] Falcó V, Almirante B, Jordano Q, Calonge L, del Valle O, Pigrau C, Planes AM, Gavalda J, Pahissa A. Influence of penicillin resistance on outcome in adult patients with invasive pneumococcal pneumonia: is penicillin useful against intermediately resistant strains? *J Antimicrob Chemother*. 2004 Aug;54(2):481-8. Epub 2004 Jun 23.
- [167] Yoshimine H, Oishi K, Mubiru F, Nalwoga H, Takahashi H, Amano H, Ombasi P, Watanabe K, Joloba M, Aisu T, Ahmed K, Shimada M, Mugerwa R, Nagatake T. Community-acquired pneumonia in Ugandan adults: short-term parenteral ampicillin therapy for bacterial pneumonia. *Am J Trop Med Hyg*. 2001 Mar-Apr;64(3-4):172-7.
- [168] Arlotti M, Zoboli G, Moscatelli GL, Magnani G, Maserati R, Borghi V, Andreoni M, Libanore M, Bonazzi L, Piscina A, Ciammarughi R. *Rhodococcus equi* infection in HIV-positive subjects: a retrospective analysis of 24 cases. *Scand J Infect Dis*. 1996;28(5):463-7.
- [169] Perelló R, Miró O, Marcos MA, Almela M, Bragulat E, Sánchez M, Agustí C, Miro JM, Moreno A. Predicting bacteremic pneumonia in HIV-1-infected patients consulting the ED. *Am J Emerg Med*. 2010 May;28(4):454-9. Epub 2010 Mar 25.
- [170] Manno D, Puoti M, Signorini L, Lapadula G, Cadeo B, Soavi L, Parainfo G, Allegri R, Cristini G, Viale P, Carosi G. Risk factors and clinical characteristics associated with hospitalization for community-acquired bacterial pneumonia in HIV-positive patients according to the presence of liver cirrhosis. *Infection*. 2009 Aug;37(4):334-9. Epub 2009 Jul 23
- [171] Malinis M, Myers J, Bordon J, Peyrani P, Kapoor R, Nakamatzu R, Lopardo G, Torres A, Feldman C, Allen M, Arnold F, Ramirez J. Clinical outcomes of HIV-infected patients hospitalized with bacterial community-acquired pneumonia. *Int J Infect Dis*. 2010 Jan;14(1):e22-7. Epub 2009 Jul 7.
- [172] Mwachari CW, Nduba VN, Park DR, Meier AS, Kariuki JN, Muyodi JA, Karimi F, Kigo A, Holmes KK, Cohen CR. Clinical presentation among HIV-infected and non-infected adults with community acquired pneumonia in Nairobi. *Int J Tuberc Lung Dis*. 2006 May;10(5):516-22.
- [173] Barbier F, Coquet I, Legriel S, Pavie J, Darmon M, Mayaux J, Molina JM, Schlemmer B, Azoulay E. Etiologies and outcome of acute respiratory failure in HIV-infected patients. *Intensive Care Med*. 2009 Oct;35(10):1678-86. Epub 2009 Jul 3.

- [174] Pedro-Botet ML, Sopena N, García-Cruz A, Mateu L, García-Núñez M, Rey-Joly C, Sabrià M. Streptococcus pneumoniae and Legionella pneumophila pneumonia in HIV-infected patients. *Scand J Infect Dis.* 2007;39(2):122-8.
- [175] Sureka A, Parada JP, Deloria-Knoll M, Chmiel JS, Phan L, Lyons TM, Ali S, Yarnold PR, Weinstein RA, Dehovitz JA, Jacobson JM, Goetz MB, Campo RE, Berland D, Bennett CL, Uphold CR. HIV-related pneumonia care in older patients hospitalized in the early HAART era *Eur Respir J. AIDS Patient Care STDS.* 2004 Feb;18(2):99-107.
- [176] Madeddu G, Porqueddu EM, Cambosu F, Saba F, Fois AG, Pirina P, Mura MS. Bacterial community acquired pneumonia in HIV-infected inpatients in the highly active antiretroviral therapy era. *Infection.* 2008 Jun;36(3):231-6. Epub 2008 May 10.
- [177] Sanders KM, Marras TK, Chan CK. Pneumonia severity index in the immunocompromised. *Can Respir J.* 2006 Mar;13(2):89-93.
- [178] Cordero E, Pachón J, Rivero A, Girón JA, Gómez-Mateos J, Merino MD, Torres-Tortosa M, González-Serrano M, Aliaga L, Collado A, Hernández-Quero J, Barrera A, Nuño E. The Grupo Andaluz para el Estudio de las Enfermedades Infecciosas. Community-acquired bacterial pneumonia in human immunodeficiency virus-infected patients: validation of severity criteria. *Am J Respir Crit Care Med.* 2000 Dec;162(6):2063-8.
- [179] Curran A, Falcó V, Crespo M, Martínez X, Ribera E, Villar del Saz S, Imaz A, Coma E, Ferrer A, Pahissa A. Bacterial pneumonia in HIV-infected patients: use of the pneumonia severity index and impact of current management on incidence, aetiology and outcome. *HIV Med.* 2008 Oct;9(8):609-15. Epub 2008 Jun 28.
- [180] Teshale EH, Hanson D, Flannery B, Phares C, Wolfe M, Schuchat A, Sullivan P. Effectiveness of 23-valent polysaccharide pneumococcal vaccine on pneumonia in HIV-infected adults in the United States, 1998–2003. *Vaccine.* 2008 Oct 29;26(46):5830-4. Epub 2008 Sep 9.
- [181] Breiman RF, Keller DW, Phelan MA, Sniadack DH, Stephens DS, Rimland D, Farley MM, Schuchat A, Reingold AL. Evaluation of effectiveness of the 23-valent pneumococcal capsular polysaccharide vaccine for HIV-infected patients. *Arch Intern Med.* 2000 Sep 25;160(17):2633-8.
- [182] Rodríguez-Barradas MC, Goulet J, Brown S, Goetz MB, Rimland D, Simberkoff MS, Crothers K, Justice AC. Impact of pneumococcal vaccination on the incidence of pneumonia by HIV infection status among patients enrolled in the Veterans Aging Cohort 5-Site Study. *Clin Infect Dis.* 2008 Apr 1;46(7):1093-100.
- [183] López-Palomo C, Martín-Zamorano M, Benítez E, Fernández-Gutiérrez C, Guerrero F, Rodríguez-Iglesias M, Girón-González JA. Pneumonia in HIV-infected patients in the HAART era: incidence, risk, and impact of the pneumococcal vaccination. *J Med Virol.* 2004 Apr;72(4):517-24.
- [184] French N, Gilks CF, Mujugira A, Fasching C. Pneumococcal vaccination in HIV-1-infected adults in Uganda: humoral response and two vaccine failures *AIDS.* 1998 Sep 10;12(13):1683-9.
- [185] French N, Nakiyingi J, Carpenter LM, Lugada E, Watera C, Moi K, Moore M, Antvelink D, Mulder D, Janoff EN, Whitworth J, Gilks CF. 23-valent pneumococcal polysaccharide vaccine in HIV-1-infected Ugandan adults: double-blind, randomised and placebo controlled trial. *Lancet.* 2000 Jun 17;355(9221):2106-11.
- [186] French N, Gordon SB, Mwalukomo T, White SA, Mwafulirwa G, Longwe H, Mwaiponya M, Zijlstra EE, Molyneux ME, Gilks CF. A trial of a 7-valent

- pneumococcal conjugate vaccine in HIV-infected adults. *N Engl J Med.* 2010 Mar 4;362(9):812-22.
- [187] Maynard M, Lièvre L, Sow PS, Kony S, Gueye NF, Bassène E, Metro A, Ndoye I, Ba DS, Coulaud JP, Costagliola D; SIDA Study Group. Primary prevention with cotrimoxazole for HIV-1-infected adults: results of the pilot study in Dakar, Senegal. *J Acquir Immune Defic Syndr.* 2001 Feb 1;26(2):130-6.
- [188] DiRienzo AG, van Der Horst C, Finkelstein DM, Frame P, Bozzette SA, Tashima KT. Efficacy of trimethoprim-sulfamethoxazole for the prevention of bacterial infections in a randomized prophylaxis trial of patients with advanced HIV infection. *AIDS Res Hum Retroviruses.* 2002 Jan 20;18(2):89-94.
- [189] Shebl FM, Engels EA, Goedert JJ, Chaturvedi AK. Pulmonary infections and risk of lung cancer among persons with AIDS. *J Acquir Immune Defic Syndr.* 2010 Nov 1;55(3):375-9.
- [190] Gil Suay V, Cordero PJ, Martínez E, Soler JJ, Perpiñá M, Greses JV, Sanchis J. Parapneumonic effusions secondary to community-acquired bacterial pneumonia in human immunodeficiency virus-infected patients. *Eur Respir J.* 1995 Nov;8(11):1934-9.
- [191] Richard E Chaisson, Neil Martinson. Tuberculosis in Africa- Combating an HIV driven crisis. *NEJM* 2008;358(11): 1089-1092
- [192] The changing incidence of AIDS events in patients receiving highly active antiretroviral therapy. *The antiretroviral therapy collaboration.* *Arch Intern Med* 2005; 165: 416-423
- [193] Grabar S, Lanoy E, Allavena C, Mary-Krause M, Bentata M, Fischer P, Mahamat A, Rabaud C, Costagliola D; on behalf of the Clinical Epidemiology Group of the French Hospital Database on HIV. Causes of the first AIDS-defining illness and subsequent survival before and after the advent of combined antiretroviral therapy. *HIV Med.* 2008 Apr;9(4):246-256.
- [194] De Cock KM, Chairsson RE. Will DOTS do it? A reappraisal of tuberculosis control in countries with high rates of HIV infection. *Int J Tuberc Lung Dis* 1999; 3: 457-465
- [195] Harries AD. Tuberculosis and human immunodeficiency infection in developing countries. *Lancet* 1990; 335: 387-390
- [196] Brandli O, *The clinical presentation of tuberculosis.* *Respiration* 1998;65: 97-105
- [197] Koppaka R, Bock N. How reliable is chest radiography? In Frieden TR ed. *Tomans tuberculosis, case detection, treatment and monitoring*, 2nd edition WHO, 2004: 51-60
- [198] Post F, Wood R, Pillay GP. Pulmonary tuberculosis in HIV infection: radiographic appearance is related to CD + T cell count. *Tuberc Lung Dis* 1995; 76(6): 518-521
- [199] Perlman DC, El-Sadr W, Nelson ET et al. Variation of chest radiographic patterns in pulmonary tuberculosis by degree of human immunodeficiency virus related immunosuppression. The Terry Bein Community Programs for Clinical Research in AIDS (CPCRA). The AIDS Clinical Trials Group (ACTG). *Clin Infect Dis* 1997; 25(2): 242-246
- [200] Behr MA, Warren SA, Salaon H. Transmission of *Mycobacterium tuberculosis* from patients smear negative for acid fast bacilli. *Lance* 1999; 353: 444-49
- [201] Grzybowski S, Barnett GD, Styblo K. Contacts of active pulmonary tuberculosis. *Bull Int Union Tuberc* 1975; 50: 90-106

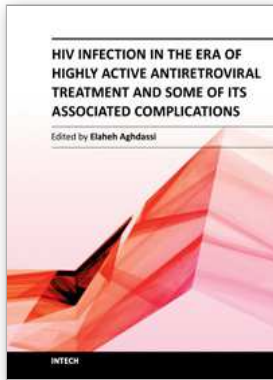
- [202] Elliot AM, Namaambo K, Allen BW et al. Negative sputum smear results in HIV positive patients with pulmonary tuberculosis in Lusaka, Zambia. *Tuberc Lung Dis* 1993; 74: 191-94
- [203] Mase SR, Ramsay A, Ng V et al. Yield of serial sputum specimen examinations in the diagnosis of pulmonary tuberculosis: a systematic review. *Int J tuberc Lung Dis* 2007;11(5): 485-95
- [204] Rawat J, Biswas D, Sindhwani G, Masih V. An alternative 1-day smear microscopy protocol for the diagnosis of pulmonary tuberculosis. *Respirology*. 2010 Oct;15(7):1127-30. doi: 10.1111/j.1440-1843.2010.01827.x.
- [205] Steingart KR, Ng V, Henry M et al. Sputum processing methods to improved the sensitivity of smear microscopy for tuberculosis: a systematic review. *Lancet Infect Dis* 2006; 6: 664-674
- [206] Steingart KR, Henry M, Ng V et al. Fluorescence versus conventional sputum smear microscopy for tuberculosis: a systematic review. *Lancet Infect Dis* 2006; 6: 571 -81
- [207] Luis Eduardo Cuevas, Najila Al -Sonboli, Lovett Lawson et al. LED Fluorescence microscopy for the diagnosis of pulmonary tuberculosis: a multi country cross sectional evaluation. *Plos Medicine* 2011; 8(7): e 1001057.doi e10.1371/journal.pmed.1001057
- [208] Crucian M, Scarparo C, Malena M et al. Meta analysis of BACTEC MGIT 960 and BACTEC 460 TB with or without solid media for the detection of Mycobacteria. *J Clin Micobiol* 2004; 42: 2321 - 2325
- [209] Madhukar Pai, Jessica Minion, Karen Steingart and Andrew Ramsay. New and improved tuberculosis diagnostics : evidence, policy, practice and impact. *Current Opinion in Pul Med* 2010; 16: 271 -284
- [210] World Health Organization. Report of the 9th meeting of the Strategic and Technical Advisory Group on TB (STAG -TB) Geneva: World Health Organization; 2009. <http://www.who.int/tb/advisory-bodies/stag/en/index.html>
- [211] Catharina Boehme, Pamela Nabeta, Doris Hilleman et al. Rapid molecular detection of tuberculosis and rifampicin resistance. *NEJM* 2010 Sept 9; 363 (11): 1005 -15
- [212] Boehme CC, Nicol MP, Nabeta P, Michael JS, Gotuzzo E, Tahirli R, Gler MT, Blakemore R, Worodria W, Gray C, Huang L, Caceres T, Mehdiyev R, Raymond L, Whitelaw A, Sagadevan K, Alexander H, Albert H, Cobelens F, Cox H, Alland D, Perkins MD. Feasibility, diagnostic accuracy, and effectiveness of decentralised use of the Xpert MTB/RIF test for diagnosis of tuberculosis and multidrug resistance: a multicentre implementation study. *Lancet*. 2011 Apr 30;377(9776):1495-505. Epub 2011 Apr 18.
- [213] World Health Organization, Strategic and Technical Advisory Group for TB, Meeting report 2010
- [214] Steingart KR, Henry M, Laal S et al. Commercial serological antibody detection tests for the diagnosis of of pulmonary tuberculosis: a systematic review. *Plos Med* 2007; 4: e202
- [215] Treatment of Tuberculosis: Guidelines for National Programmes. WHO. WHO/HTM/2009.420
- [216] Faiz A Khan, Jessica Minion, Madhular Pai et al. Treatment of active tuberculosis in HIV co-infected patients: a systematic review and meta- analysis. *Clin Infect Dis* 2010; 50(9): 1288-1299

- [217] I. Dubrovina, K. Miskinis, S. Lyepshina et al. Drug resistant tuberculosis and HIV in Ukraine: a threatening convergence of two epidemics. *Int J Tuberc Lung Dis* 2008; 12(7): 758-762.
- [218] Charles D. Wells, J.Peter Cegielski, Lisa J. Nelson et al. HIV Infection and Multi drug resistant tuberculosis – the perfect storm. *Journal of Infectious Diseases* 2007; 196: S86-107
- [219] Gandhi NR, Moll A, Sturm AW et al. Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. *Lancet* 2006 Nov 4;368(9547):1575-80.
- [220] Kangombe CT, Harries AD, Ito K et al. Long term outcome in patients registered with tuberculosis in Zomba, Malawi : mortality at 7 years according to initial HIV status and type of TB. *Int J. Tuberc Lung Dis* 2004; 8: 829 -836
- [221] Salim S. Abdool Karim, Kogieleum Naidoo, Anneke Grobler et al. Timing of initiation of anti -retroviral drugs during tuberculosis therapy. *N Eng J Med* 2010; 362: 697 -706.
- [222] Wiktor SZ, Sassin Maroko M, Grant AD et al. Efficacy of trimethoprim sulphamethoxazole prophylaxis to decrease morbidity and mortality in HIV1 infected patients with tuberculosis in Abidjan, Cote d'Ivoire: a randomized controlled trial. *Lancet* 1999; 353: 1469-1475
- [223] Woldehanna S, Volmink J. Treatment of latent tuberculosis infection in HIV infected persons(Review). *Cochrane Database of Systematic Reviews* 2004, Issue 1. Art. No.: CD 000171.DOI:10. 1002/14651858.CD000172.pub2
- [224] Enrico Girardi, Caroline A Sabin, Antonell d' Amino Montarte et al Incidence of tuberculosis among HIV infected patients receiving highly active antiretroviral therapy in Europe and North America. *Clinical Infectious Diseases* 2005; 41: 1772-82
- [225] Badri M, Wilson D, Wood R. Effect of highly active anti-retroviral therapy on the incidence of tuberculosis in South Africa: a cohort study. *Lancet* 2002; 359(9323): 2059-2064.
- [226] Jonathan E Golub, Valeria Saracen, Solange C Covalcante et al. The impact of antiretroviral therapy and Isoniazid preventive therapy on tuberculosis incidence in HIV infected patients in Rio de Janeiro, Brazil. *AIDS* 2007, 21: 1441-144
- [227] World Health Organization. Policy on Collaborative TB/HIV Activities, 2011.
- [228] Diagnosis and treatment of disease caused by non tuberculous mycobacteria. Official statement of the American Thoracic Society. *Am J Respir Crit Care Med* 1997; 156: S1-S25
- [229] Raju B, Schluger NW. Significance of respiratory isolates of *Mycobacterium avium* complex in HIV-positive and HIV-negative patients. *Int J Infect Dis.* 2000;4(3):134-9.
- [230] MacDonell KB, Glassroth J. *Mycobacterium avium* complex and other nontuberculous mycobacteria in patients with HIV infection. *Semin Respir Infect.* 1989 Jun;4(2):123-32.
- [231] Zhao GG, Li JY, Atlas E, Cleary JP. Cytomegalovirus pneumonitis as an initial presentation in an HIV-infected patient. *Conn Med.* 1999 Oct;63(10):585-8.
- [232] Rodriguez-Barradas MC, Stool E, Musher DM, Gathe J Jr, Goldstein J, Genta RM, Yoffe B. Diagnosing and treating cytomegalovirus pneumonia in patients with AIDS *Clin Infect Dis.* 1996 Jul;23(1):76-81.
- [233] Salomon N, Gomez T, Perlman DC, Laya L, Eber C, Mildvan D. Clinical features and outcomes of HIV-related cytomegalovirus pneumonia. *AIDS.* 1997 Mar;11(3):319-24.

- [234] Dore GJ, Marriott DJ, Duflou JA. Clinico-pathological study of cytomegalovirus (CMV) in AIDS autopsies: under-recognition of CMV pneumonitis and CMV adrenalitis. *Aust N Z J Med.* 1995 Oct;25(5):503-6.
- [235] d'Arminio Monforte A, Vago L, Lazzarin A, Boldorini R, Bini T, Guzzetti S, Antinori S, Moroni M, Costanzi G.. AIDS-defining diseases in 250 HIV-infected patients; a comparative study of clinical and autopsy diagnoses. *AIDS.* 1992 Oct;6(10):1159-64.
- [236] Lyles RH, Chu C, Mellors JW, Margolick JB, Detels R, Giorgi JV, Al-Shboul Q, Phair JP. Prognostic value of plasma HIV RNA in the natural history of *Pneumocystis carinii* pneumonia, cytomegalovirus and *Mycobacterium avium* complex. Multicenter AIDS Cohort Study. *AIDS.* 1999 Feb 25;13(3):341-9.
- [237] de la Hoz RE, Byrne SK, Hayashi S, Sherlock C, Cook D, Hogg JC. Diagnosis of cytomegalovirus infection in HIV-infected patients with respiratory disease. *Clin Diagn Virol.* 1998 May 1;10(1):1-7.
- [238] Youle MS, Gazzard BG, Johnson MA, Cooper DA, Hoy JF, Busch H, Ruf B, Griffiths PD, Stephenson SL, Dancox M, et al. Effects of high-dose oral acyclovir on herpesvirus disease and survival in patients with advanced HIV disease: a double-blind, placebo-controlled study. European-Australian Acyclovir Study Group. *AIDS.* 1994 May;8(5):641-9.
- [239] Umar SH, Kanth A. Disseminated cutaneous herpes simplex virus type-1 with interstitial pneumonia as a first presentation of AIDS. *J Natl Med Assoc.* 1999 Aug;91(8):471-4.
- [240] Calore EE. Herpes simplex type 2 pneumonia. *Braz J Infect Dis.* 2002 Dec;6(6):305-8. Epub 2003 Nov 3.
- [241] Fraisse P, Faller M, Rey D, Labouret N, Partisani M, Stoll-Keller F, Lang JM, Weitzenblum E. Recurrent varicella pneumonia complicating an endogenous reactivation of chickenpox in an HIV-infected adult patient. *Eur Respir J.* 1998 Mar;11(3):776-8..
- [242] Resnick L, Pitchenik AE, Fisher E, Croney R. Detection of HTLV-III/LAV - Specific IgG and antigen in bronchoalveolar lavage fluid from two patients with Lymphocytic interstitial pneumonitis associated AIDS related complex. *AM J Med* 1987 Mar; 82(3): 553-6
- [243] Travis WD, Fox CG, Devaney KO et al. Lymphoid pneumonitis in 50 adult patients infected with the human immunodeficiency virus: lymphocytic interstitial pneumonitis versus non specific interstitial pneumonitis. *Hum Pathol* 1992; 23: 529-41
- [244] Guillon JM, Autran B, Denis M, Fouret P, Plata F, Mayaud CM, Akoun GM. Human immunodeficiency virus-related lymphocytic alveolitis. *Chest.* 1988 Dec;94(6):1264-70.
- [245] response Itescu S, Brancato LJ, Buxbaum J, Gregersen PK, Rizk CC, Croxson TS, Solomon GE, Winchester R. A diffuse infiltrative CD8 lymphocytosis syndrome in human immunodeficiency virus (HIV) infection: a host immune response associated with HLA-DR5. *Ann Intern Med.* 1990 Jan 1;112(1):3-10.
- [246] Detection of HTLV-III/LAV-specific IgG and antigen in bronchoalveolar lavage fluid from two patients with lymphocytic interstitial pneumonitis associated with AIDS-related complex.
- [247] Ingiliz P, Appenrodt B, Gruenhage F, Vogel M, Tschampa H, Tasci S, Rockstroh JK. Lymphoid pneumonitis as an immune reconstitution inflammatory syndrome in a patient with CD4 cell recovery after HAART initiation. *HIV Med.* 2006 Sep;7(6):411-4.

- [248] Ripamonti D, Rizzi M, Maggiolo F, Arici C, Suter F. Resolution of lymphocytic interstitial pneumonia in a human immunodeficiency virus-infected adult following the start of highly active antiretroviral therapy. *Scand J Infect Dis.* 2003;35(5):348-51.
- [249] Dufour V, Wislez M, Bergot E, Mayaud C, Cadranel J. Improvement of symptomatic human immunodeficiency virus-related lymphoid interstitial pneumonia in patients receiving highly active antiretroviral therapy. Case reports and series indicate good responses to treatment with HAART. *Clin Infect Dis.* 2003 May 15;36(10):e127-30. Epub 2003 May 6.
- [250] Basu D, Williams FM, Ahn CW, Reveille JD. Changing spectrum of the diffuse infiltrative lymphocytosis syndrome. *Arthritis Rheum.* 2006 Jun 15;55(3):466-72.
- [251] Sattler F, Nichols L, Hirano L, Hiti A, Hofman F, Hughlett C, Zeng L, Boylen CT, Koss M. Nonspecific interstitial pneumonitis mimicking *Pneumocystis carinii* pneumonia. *Am J Respir Crit Care Med.* 1997 Sep;156(3 Pt 1):912-7.
- [252] Griffiths MH, Miller RF, Semple SJ. Interstitial pneumonitis in patients infected with the human immunodeficiency virus. *Thorax.* 1995 Nov;50(11):1141-6.
- [253] Ognibene FP, Masur H, Rogers P, Travis WD, Suffredini AF, Feuerstein I, Gill VJ, Baird BF, Carrasquillo JA, Parrillo JE, et al. Nonspecific interstitial pneumonitis without evidence of *Pneumocystis carinii* in asymptomatic patients infected with human immunodeficiency virus (HIV). *Ann Intern Med.* 1988 Dec 1;109(11):874-9.
- [254] Rodríguez-Rosado R, Soriano V, Dona C, González-Lahoz Opportunistic infections shortly after beginning highly active antiretroviral therapy. *J. Antivir Ther.* 1998;3(4):229-31.
- [255] Mori S, Polatino S, Estrada-Y-Martin RM. *Pneumocystis*-associated organizing pneumonia as a manifestation of immune reconstitution inflammatory syndrome in an HIV-infected individual with a normal CD4+ T-cell count following antiretroviral therapy. *Int J STD AIDS.* 2009 Sep;20(9):662-5.
- [256] Jagannathan P, Davis E, Jacobson M, Huang L Life-threatening immune reconstitution inflammatory syndrome after *Pneumocystis* pneumonia: a cautionary case series. *AIDS.* 2009 Aug 24;23(13):1794-6
- [257] Jenny-Avital ER, Abadi M. Immune reconstitution cryptococcosis after initiation of successful highly active antiretroviral therapy. *Clin Infect Dis.* 2002 Dec 15;35(12):e128-33. Epub 2002 Nov 20.
- [258] Janda S, Quon BS, Swiston J. HIV and pulmonary arterial hypertension: a systematic review. *HIV Med.* 2010 Nov;11(10):620-34. doi: 10.1111/j.1468-1293.2010.00829.x.
- [259] Degano B, Guillaume M, Savale L, Montani D, Jaïs X, Yaici A, Le Pavec J, Humbert M, Simonneau G, Sitbon O. HIV-associated pulmonary arterial hypertension: survival and prognostic factors in the modern therapeutic era. *AIDS.* 2010 Jan 2;24(1):67-75.
- [260] Polish LB, Cohn DL, Ryder JW, Myers AM, O'Brien RF. Pulmonary non-Hodgkin's lymphoma in AIDS. *Chest.* 1989 Dec;96(6):1321-6.
- [261] Shiels MS, Cole SR, Mehta SH, Kirk GD. Lung cancer incidence and mortality among HIV-infected and HIV-uninfected injection drug users. *J Acquir Immune Defic Syndr.* 2010 Dec 1;55(4):510-5.
- [262] Shebl FM, Engels EA, Goedert JJ, Chaturvedi AK. Pulmonary infections and risk of lung cancer among persons with AIDS. *J Acquir Immune Defic Syndr.* 2010 Nov 1;55(3):375-9.

- [263] Nutankalva L, Wutoh AK, McNeil J, Frederick WR, Reddy RB, Daftary M, Gentles A, Addae-Afoakwa K. Malignancies in HIV: pre- and post-highly active antiretroviral therapy. *J Natl Med Assoc.* 2008 Jul;100(7):817-20.
- [264] Levine AM, Seaberg EC, Hessol NA, Preston-Martin S, Silver S, Cohen MH, Anastos K, Minkoff H, Orenstein J, Dominguez G, Watts DH. HIV as a risk factor for lung cancer in women: data from the Women's Interagency HIV Study. *J Clin Oncol.* 2010 Mar 20;28(9):1514-9. Epub 2010 Feb 22.
- [265] D'Jaen GA, Pantanowitz L, Bower M, Buskin S, Neil N, Greco EM, Cooley TP, Henry D, Stem J, Dezube BJ, Stebbing J, Aboulaflia DM. Human immunodeficiency virus-associated primary lung cancer in the era of highly active antiretroviral therapy: a multi-institutional collaboration. *Clin Lung Cancer.* 2010 Nov 1;11(6):396-404.
- [266] Tirelli U, Spina M, Sandri S, Serraino D, Gobitti C, Fasan M, Sinicco A, Garavelli P, Ridolfo AL, Vaccher E. Lung carcinoma in 36 patients with human immunodeficiency virus infection. The Italian Cooperative Group on AIDS and Tumors. *Cancer.* 2000 Feb 1;88(3):563-9.
- [267] Gingo MR, George MP, Kessinger CJ, Lucht L, Rissler B, Weinman R, Slivka WA, McMahon DK, Wenzel SE, Sciruba FC, Morris A. Pulmonary function abnormalities in HIV-infected patients during the current antiretroviral therapy era. *Am J Respir Crit Care Med.* 2010 Sep 15;182(6):790-6. Epub 2010 Jun 3.
- [268] Drummond MB, Kirk GD, Ricketts EP, McCormack MC, Hague JC, McDyer JF, Mehta SH, Engels EA, Wise RA, Merlo CA. Cross sectional analysis of respiratory symptoms in an injection drug user cohort: the impact of obstructive lung disease and HIV. *BMC Pulm Med.* 2010 May 11;10:27.
- [269] Sanito NJ, Morley TF, Condoluci DV. Bronchiolitis obliterans organizing pneumonia in an AIDS patient. *Eur Respir J.* 1995 Jun;8(6):1021-4
- [270] Tobin-D'Angelo MJ, Hoteit MA, Brown KV, Ray SM, King MD. Dapsone-induced hypersensitivity pneumonitis mimicking *Pneumocystis carinii* pneumonia in a patient with AIDS. *Am J Med Sci.* 2004 Mar;327(3):163-5.
- [271] Behrens GM, Stoll M, Schmidt RE. Pulmonary hypersensitivity reaction induced by efavirenz. *Lancet.* 2001 May 12;357(9267):1503-4.
- [272] Morris AM, Nishimura S, Huang L. Subacute hypersensitivity pneumonitis in an HIV infected patient receiving antiretroviral therapy. *Thorax.* 2000 Jul;55(7):625-7.
- [273] Naccache JM, Antoine M, Wislez M, Fleury-Feith J, Oksenhendler E, Mayaud C, Cadranet. Sarcoid-like pulmonary disorder in human immunodeficiency virus-infected patients receiving antiretroviral therapy. *JAMA J Respir Crit Care Med.* 1999 Jun;159(6):2009-13.
- [274] Lenner R, Bregman Z, Teirstein AS, DePalo L. Recurrent pulmonary sarcoidosis in HIV-infected patients receiving highly active antiretroviral therapy. *Chest.* 2001 Mar;119(3):978-81.
- [275] Nan DN, Fernández-Ayala M, Iglesias L, García-Palomo D, Parra JA, Fariñas MC. Talc granulomatosis. A differential diagnosis of interstitial lung disease in HIV patients. *Chest.* 2000 Jul;118(1):258-60.



HIV Infection in the Era of Highly Active Antiretroviral Treatment and Some of Its Associated Complications

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Human immunodeficiency virus (HIV) infection is a complex illness affecting the immune system. Acquired immunodeficiency syndrome (AIDS) is an advanced form of HIV infection in which the patient has developed opportunistic infections or certain types of cancer and/or the CD4+ T cell count has dropped below 200/ μ L. More than 40 million persons around the world are infected with HIV, with approximately 14,000 new infections every day. The disease causes 3 million deaths worldwide each year, 95% of them in developing countries. Optimal management of human immunodeficiency virus requires strict adherence to highly active antiretroviral treatment (HAART) regimens, but the complexity of these regimens (e.g., pill burden, food requirements, drug interactions, and severe adverse effects) limits effective treatment. However, more patients with HIV are surviving longer today because of these drugs. This allows further study of commonly associated adverse effects. These may affect all body systems and range from serious toxicities to uncomfortable but manageable events. This book reviews some of HAART-related metabolic and neurological complications.

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